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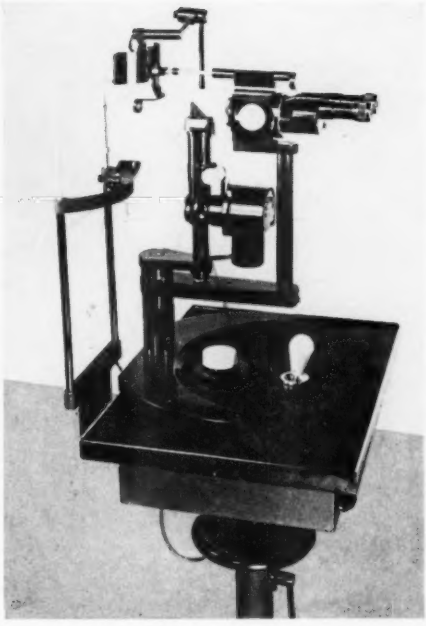

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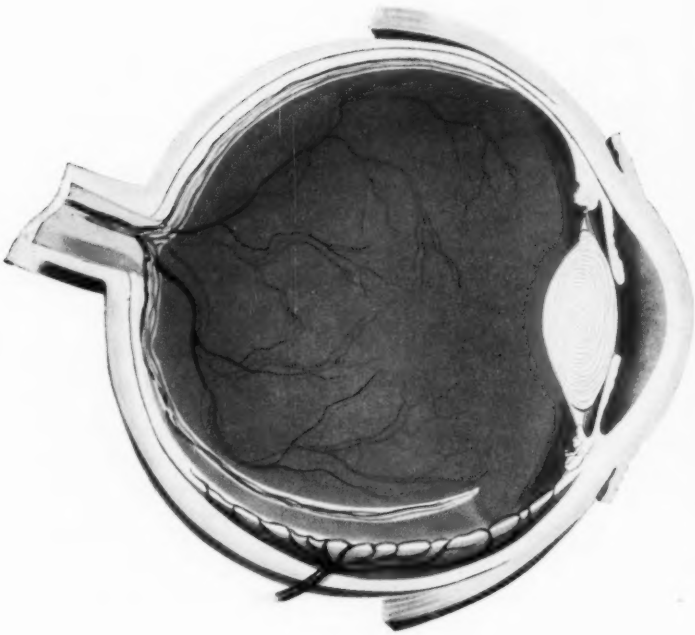

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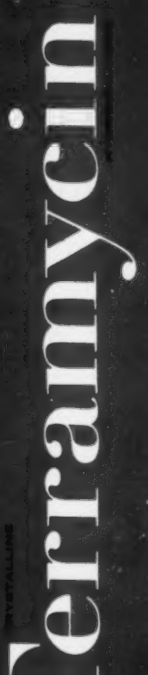

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1. Minor, T., et al.: *Antibiotics & Chemotherapy* 1:251 (July) 1951.
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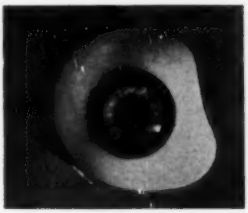

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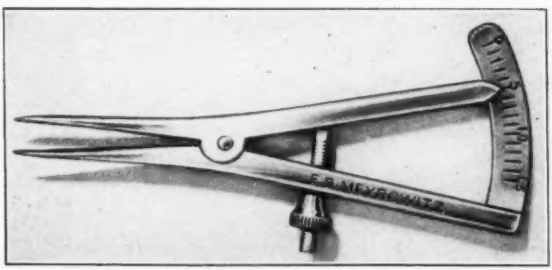

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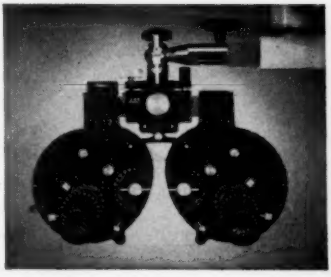

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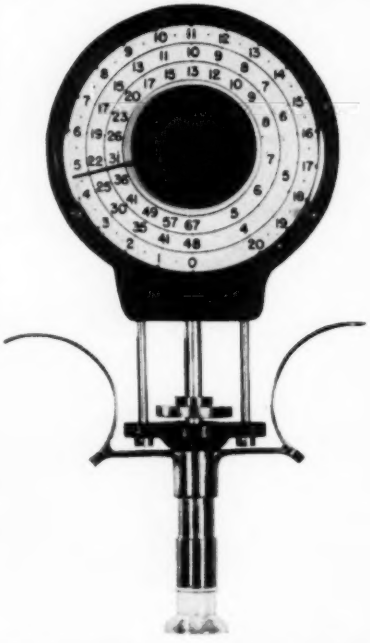

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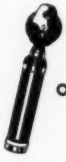

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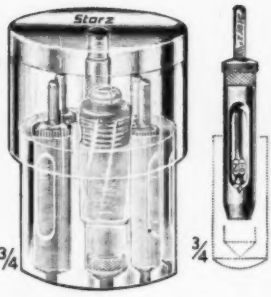

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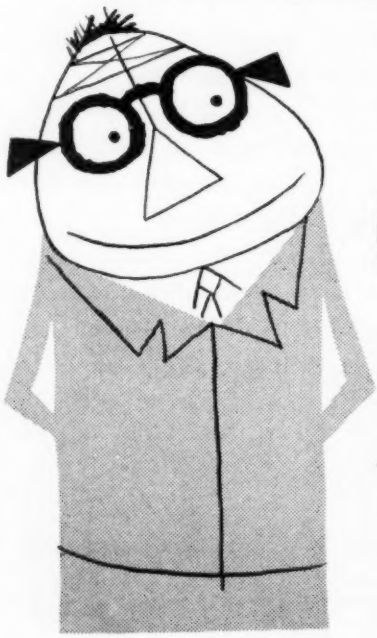

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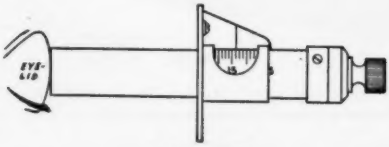

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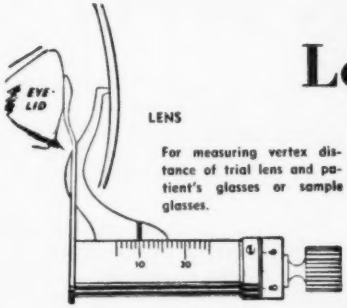

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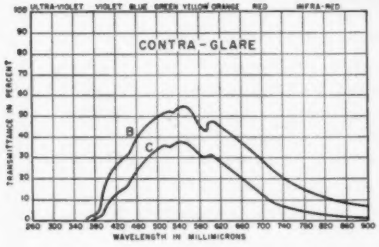

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Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S.: *Proc. Staff Mtgs., Mayo Clinic* 26: 361, September 26, 1951.

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REPRESENTATION OF CORNEAL AND CONJUNCTIVAL SENSATION IN THE CENTRAL NERVOUS SYSTEM

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AND
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BOSTON

THE CORNEA has generally been believed to have the property of receiving pain but not touch sensation. Thus, a wisp of cotton or a fine hair elicits a distinctly unpleasant sensation when it touches the cornea, and graded test objects are said to elicit no other type of sensation.[1] Moreover, tactile end-organs have never been found in the cornea,[2] and there is indirect evidence, such as absence of vibration sense and the uniform rate of cocaine-induced anesthesia, that is said to indicate absence of touch sensation in the cornea. But, as indicated in a recent review by Adler,[3] the evidence is not unequivocal, and recent observations by neurosurgeons [4] on patients who have had the trigeminal tractotomy of Sjöqvist [5] have shown uniformly a persistence of nonpainful sensation in the cornea with loss of pain and temperature sensation in the face. This finding has been interpreted as indicating the presence of tactile sensitivity in the cornea. Curiously, little evidence has been adduced from data on the representation within the central nervous system. Accordingly, it seemed desirable to record the present observations on a patient with lateral medullary thrombosis which have led to the conclusion that all corneal sensation, whatever its nature may be, is represented in

From the Howe Laboratory of Ophthalmology, Harvard University Medical School, and the Massachusetts Eye and Ear Infirmary.

1. (*a*) Frey, M., and Strughold, H.: Weitere Untersuchungen über das Verhalten von Hornhaut und Bindehaut des menschlichen Auges gegen Berührungsreize, Ztschr. Biol. **84**:321-334, 1926. (*b*) Strughold, H.: The Mechanical Threshold of the Cornea Reflex of the Usual Laboratory Animals, Am. J. Physiol. **94**:235-246, 1930. (*c*) Eckardt, L. B.; McLean, J. M., and Goodell, H.: Experimental Studies on Headache: The Genesis of Pain from the Eye, A. Res. Nerv. & Ment. Dis., Proc. **23**:209-227, 1943, 1943. (*d*) Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

2. It should be noted, however, that E. Zander and G. Weddell (Observations on the Innervation of the Cornea, J. Anat. **85**:68-99, 1951) suggest that the bare nerve endings in the corneal stroma may be responsible for the alleged tactile sensibility.

3. Adler, F. H.: Physiology of the Eye, St. Louis, C. V. Mosby Company, 1950.

4. Rowbotham, G. F.: Observation on the Effects of Trigeminal Denervation, Brain **62**: 364-379, 1939. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:498-509 (March) 1940. Falconer, M. A.: Intramedullary Trigeminal Tractotomy and Its Place in the Treatment of Facial Pain, J. Neurol., Neurosurg. & Psychiat. **12**:297-311, 1949. Walker, A. E., in discussion on Eckardt, McLean, and Goodell.[1c] Sweet, W.: Personal communication to the authors.

5. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve, Acta psychiat. et neurol. (Supp.) **17**:1, 1938.

the brain stem along with the facial representation of sensation for pain and temperature rather than with that for touch. The present case also permitted correlative observations to be made on conjunctival sensation, which has received little attention from the point of view of representation in the central nervous system. Although the case is not unique—in fact, it is a typical manifestation of the syndrome [6]—we are not aware of the findings having previously been utilized to locate the representation of corneoconjunctival sensation in the central nervous system.

The patient in question was a man aged 69 with a clear-cut syndrome of lateral medullary (or posterior inferior cerebellar) thrombosis, characterized by right-sided cerebellar ataxia, dysphonia, nystagmus, a right-sided Horner syndrome, persistent hiccough, absence of pain and temperature sensation but preservation of touch sensation over the right side of the face, and hemianesthesia of the left side of the trunk and the left limbs. Tactile sensation was preserved on the two sides of the face and was subjectively noted to be either equal in testing with a cotton wisp or only slightly less on the right side. The onset had been sudden one week prior to the first observation and had been characterized by vertigo, ataxia, and vomiting.

Examination of the eyes, made repetitively during the second and third weeks of the illness, showed the following abnormalities consistently: The right cornea and bulbar conjunctiva were anesthetic to all test objects (cotton wisp, blunt rod, and pinprick). The upper and lower palpebral conjunctiva showed no sensation with a cotton wisp and inconstant touch sensation with pinprick. The conjunctiva of the upper lid was more sensitive than that of the lower lid. A test tube containing ice water elicited no sensation when held against the bulbar conjunctiva of the right eye and one of touch only when held against the right cheek but was noted as being cold when held against the left conjunctiva and the left cheek. A vibrating tuning fork elicited no sensation from the right bulbar conjunctiva and one of touch only from the right palpebral conjunctiva; on the left it produced a sensation of unpleasantness, but not of vibration when in contact with the bulbar conjunctiva, but a sensation of vibration when in contact with the palpebral conjunctiva.[7] Firm pressure against the right eye elicited no discomfort, whereas the same pressure exerted against the left eye caused the patient to wince with pain. No bradycardia was produced by pressure against either eye.

Thus, in this case, the loss of pain and temperature sensation in the face was accompanied by anesthesia of the cornea and bulbar conjunctiva. Since tactile sensation in the face was present to almost a normal degree, one may infer that sensation in the cornea and bulbar conjunctiva is represented in the brain stem with the facial sensation of pain (and temperature) but not of touch. Sensation in the palpebral conjunctiva, on the other hand, appears to have the same representation in the brain stem for pain, temperature, and touch as does the skin, but has a higher threshold than that of the skin. One might suggest, of course, that the center for tactile sensation had been involved in the present case by a more extensive lesion than occurs with the tractotomy, but this is not borne out by any proportionately greater involvement of tactile sensation in the face. Indeed, tactile sensation in the face was better preserved in the present case than in most of those in which the tractotomy has been done. Alternatively, one might suggest that the tractotomy procedure does not interrupt all connections between the spinal

6. The reader is referred to a review of the literature, e. g., that of Smyth (Smyth, G. E.: The Systemization and Central Connections of the Spinal Tract and Nucleus of the Trigeminal Nerve, Brain **62**:41-87, 1939).

7. It is not generally recognized that the normal conjunctiva is relatively insensitive to test objects used for detecting touch sense. Thus, wisps of cotton that cause an uncomfortable response in the cornea elicit no response when rubbed against the conjunctiva.

portion of the nucleus of the trigeminal nerve with the Gasserian ganglion and that the greatly diminished pain sensibility in the cornea is interpreted as touch. There would appear to be no way of confirming or denying such a possibility in the present state of our knowledge.

SUMMARY AND CONCLUSIONS

A case of lateral medullary thrombosis has been studied with particular reference to corneal and conjunctival sensitivity. The patient had only slight reduction of tactile sensation in the face but complete loss of pain and temperature sensation on the affected side. The cornea and the bulbar conjunctiva on the affected side were completely anesthetic and there was loss of deep pain sensibility from pressure on the eye, but the palpebral conjunctiva showed, like the skin, preservation of some sensation of touch with loss of sensation for pain and temperature. From this it is inferred that the sensation in the cornea and bulbar conjunctiva is represented in the brain stem along with the facial sensation of pain and temperature and not with that of touch.

DETECTION OF INTRAOCULAR TUMORS WITH RADIOACTIVE PHOSPHORUS

A Preliminary Report with Special Reference to Differentiation of the Cause of Retinal Separation

CHARLES I. THOMAS, M.D.
JACK S. KROHMER, M.A.
AND
JOHN P. STORAASLI, M.D.
CLEVELAND

IN RECENT studies, we have found that measurement of the uptake of radioactive phosphorus in tumor tissue can be applied as a valuable test to aid in the diagnosis of intraocular tumors in cases in which the clinical ophthalmologic evidence as to the cause of retinal separation is not conclusive. This test to date has been used in eight cases of possible tumor and has proved fairly successful. Because of the definite, although unexploited, value of the test, and because of the relatively small number of tumors which are seen, it was decided that a preliminary report should be submitted at this time.

BACKGROUND

The use of radioactive material for the localization of tumors has assumed increasing importance in recent years. In 1946, Low-Beer [1] proposed the use of radioactive phosphorus in diagnosis and localization of breast tumors. Moore and associates [2] noted a consistent affinity of brain tumors for the absorption of previously injected fluorescein and developed and synthesized diiodofluorescein (fluorescein combined with radioactive iodine—I^{131}), from which the emission of gamma radiations could be detected. After injection of this substance, he obtained higher readings with a Geiger counter over the area of the suspected tumor than he obtained over normal tissue. He found that as the dye is removed from the blood stream the counting rate tends to equalize over all parts of the brain, with the exception of the area over the tumor, where the highest counts are recorded. Woolsey and Thoma [3] corroborated Moore's findings.

This research was performed in part under AEC contract No. W-31-109-eng-78.

From the Department of Surgery, Division of Ophthalmology, and the Department of Radiology, Western Reserve University School of Medicine and University Hospitals.

1. Low-Beer, B. V. A.: Surface Measurements of Radioactive Phosphorus in Breast Tumors as Possible Diagnostic Method, Science **104**:399 (Oct. 25) 1946.

2. Moore, G. E.: (*a*) Fluorescein as an Agent in the Differentiation of Normal and Malignant Tissue, Science **106**:130-131 (Aug. 8) 1947; (*b*) Use of Radioactive Diiodofluorescein in the Diagnosis and Localization of Brain Tumors, ibid. **107**:569-571 (May 28) 1948. (*c*) Moore, G. E.; Hunter, G. W., and Hubbard, T. B.: Clinical and Experimental Studies of Fluorescein Dyes, with Special Reference to Their Use for the Diagnosis of Central Nervous System Tumors, Ann. Surg. **130**:637-642 (Oct.) 1949.

3. Woolsey, R. D., and Thoma, G. E.: Localization of Intracranial Neoplasms with Radioactive Diiodofluorescein, J. Missouri M. A. **47**:885-889 (Dec.) 1950.

More recently (1949), Selverstone and his associates [4] employed radioactive phosphorus (P^{32}) to localize brain tumors. They found that after the injection of the P^{32} the radioactivity of the tumor tissue was from 5.8 to 110 times as great as that of the adjacent normal white matter.

There is a close relation, both embryologically and histologically, between the central nervous system and the structures of the eye, so that the basic studies which have been carried out on brain tumors can be applied to the retina, choroid, and iris. In the present studies, with the use of radioactive phosphorus, a definitely increased concentration of active material was detected in tumor tissue over that found in normal tissue. This increased activity was present one-half hour after injection of the radioactive phosphorus and persisted to a somewhat slighter degree as late as 24 hours after injection. There are various possible mechanisms which will explain this increased phosphorus concentration in tumor tissue. Although probably due to a more rapid nucleic-acid turnover in fast-growing tumor tissue (Marshak,[5] Tuttle and associates [6]), the greater concentration may also be due to (1) increased vascularity of the tumor or (2) increased phosphate-ion concentration, as a result of breakdown of the blood-tissue barrier, such as that suggested by Friedemann [7] in the case of the blood-brain barrier. In any event, it is shown in this paper that in every case encountered the intraocular tumor did exhibit an increased phosphorus concentration, while in two cases (Cases 1 and 7) in which no tumor was present the activity proved to be uniformly distributed throughout the eye.

These findings indicate that the radioactive-phosphorus test may be valuable in the detection of intraocular tumors. However, this conclusion must be further investigated with more clinical tests and experimental work.

RATIONALE

The success of this type of tracer study depends upon one's ability to detect the presence of tumor tissue which has, by virtue of its accelerated rate of growth, taken up a higher concentration of tracer material than the surrounding normal tissue. Since the tumors we have studied are adjacent to the outer surface of the eye (maximal depth 5 to 7 mm.), we decided that a beta-ray-emitting tracer isotope would have a definite advantage over a gamma emitter, such as is used for detection and localization of brain tumors (I^{131} incorporated in diiodofluorescein [2b]). An outstanding advantage of using a beta emitter is that the relatively short range of the beta particles (maximum of 8 mm. in tissue for P^{32}) allows measurement of activity from a thin layer of tissue in front of the counter, thus eliminating the masking effect of the activity in the surrounding tissue, which would contribute to the total radioactive count if a gamma emitter were used.

4. Selverstone, B.; Solomon, A. K., and Sweet, W. H.: Localization of Brain Tumors by Means of Radioactive Phosphorus, J. A. M. A. **140**:277-278 (May 21) 1949. Selverstone, B.; Sweet, W. H., and Robinson, C. V.: Clinical Use of Radioactive Phosphorus in the Surgery of Brain Tumors, Ann. Surg. **130**:643-651 (Oct.) 1949.

5. Marshak, A.: P^{32} Uptake by Nuclei, J. Gen. Physiol. **25**:275-291 (Nov.) 1941.

6. Tuttle, L. W.; Erf, L. A., and Lawrence, J. H.: Studies on Neoplasms with the Aid of Radioactive Phosphorus: II. Phosphorus Metabolism of the Nucleoprotein, Phospholipid and Acid Soluble Fractions of Normal and Leukemic Mice, J. Clin. Invest. **20**:57-61 (Jan.) 1941.

7. Friedemann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125-145 (April) 1942.

The choice of radioactive phosphorus (P^{32}) for the present study was based mainly upon its selective uptake in tumor tissue and upon the fact that it is a beta emitter. An added advantage of this isotope is its half-life of 14.3 days, which makes possible an ease of handling and flexibility of test scheduling which is not possible with other, shorter-lived isotopes.

TECHNIQUE OF DIAGNOSTIC METHOD

Counting Instruments.—The in vivo counting is carried out by means of a small, thin-end-window (1.5 mg. per square centimeter) Geiger counter (Fig. 1).[8] This instrument is entirely adequate for counting measurements in the anterior half of the eyeball, and by means of rotation and fixation with sutures for traction the surface of the globe behind the equator can be exposed. In order to facilitate the counting over posterior lesions of the globe, work is in progress on a scintillation counter probe which will reach the areas now accessible with transillumination probes.

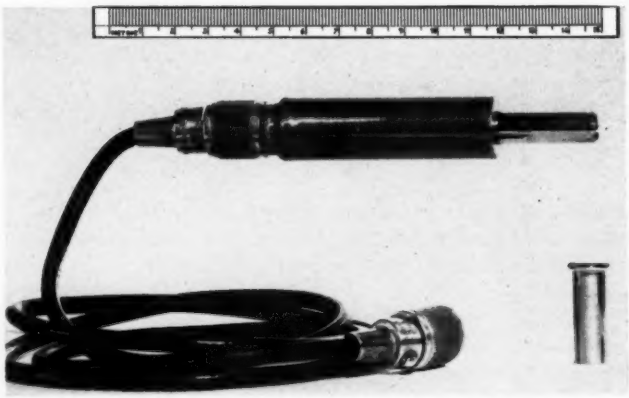

Fig. 1.—Small Geiger counter [8] used for eye measurements.

For counting in vitro, any conventional laboratory thin-window Geiger-counter apparatus is satisfactory.

Preparation of Patient.—The procedure is carried out with local anesthesia; this is produced by instillation into the conjunctival sac of 1% tetracaine hydrochloride or 4% cocaine hydrochloride. One-half hour before the counts are to be started, a 500-mc.[9] dose of P^{32} is administered intravenously in sterile isotonic solution of sodium chloride.

In Vivo Counting Procedure.—One-half hour after injection of the radioactive phosphorus, counting is carried out for one minute, with the small Geiger counter held in contact with the sclera, directly over the area of the suspected tumor (Fig. 2). This procedure is repeated at 1 hour and 1½ hours after injection of the isotope. Similar counts are made over other areas of both eyes, and the results are recorded.

8. Model *222*, made by Anton Electronic Laboratory, Inc., 1226-1238 Flushing Ave., Brooklyn 6.

9. A dose of 500 mc. of P^{32} is far below the level of radioactivity which might produce manifest injurious effects. This is relatively twice the generally accepted tolerance level, but the additional exposure is insignificant. The total radiation is less than that received during most diagnostic x-ray procedures.

In Vitro Counting Procedure.—As soon as possible after the eye is removed, it is sectioned directly through the tumor. One-half of the globe is retained for the preparation of microscopic sections and of a radioautograph, while the other portion is sectioned further, with samples removed from the tumor, the sclera, the retina, and the lens. These sections are weighed wet and placed into porcelain counting dishes, in which they are dissolved in concentrated nitric acid and then dried, thus yielding thin, flat samples. After drying, the samples are counted under identical conditions, using a conventional laboratory Geiger-counter apparatus. The results are recorded in corrected (for background radiation) counts per minute per gram of sample. It must be emphasized that counts should be made on fresh specimens. If these specimens are allowed to remain in a fixative for any length of time, there is a loss of activity from the sections by leaching.

Preparation of Radioautograph.—The half of the eye retained for slides and the radioautograph is embedded in paraffin and, after the preparation of appropriate slides, is counted at close range with a Geiger counter. The count per minute is converted into disintegrations per

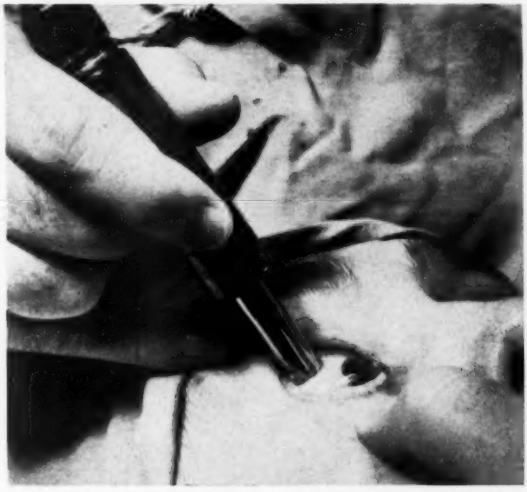

Fig. 2.—Use of Geiger counter on the living eye.

minute, using "geometry" corrections. In the darkroom procedure, the eye is placed in contact with a piece of film and subsequently wrapped in lightproof paper and placed in a refrigerator. The time of exposure is adjusted so that the product of days of exposure and the disintegration per gram per minute is from 40,000 to 70,000.

Two types of film have been used, with about equally good results: (1) Kodak® Nuclear Tract Plates NTB 3, 25 μ, and (2) Kodak® No-Screen X-Ray Film.

The exposed radioautographs are developed by inspection, using Kodak® D-19 Developer at 18 C.

REPORT OF CASES

Case 1.—A woman, aged 60, complained of disturbance of vision in the right eye, which had been present for one month. Vision in this eye measured 20/40 and was corrected to 20/30 with a hyperopic cylinder. External examination revealed no abnormality. Slit-lamp examination revealed a slight nuclear haze in the lens, but the findings were otherwise normal. Ophthalmoscopic examination showed that the media were clear. There was a large elevated area in the retina, involving the upper outer quadrant as far anteriorly as could be observed and extending

almost to the macula. This elevation was slightly pigmented in spots, and, although a few folds were present, the borders blended into the surrounding tissue gradually. No exudate was present, and no retinal tear was evident. Transillumination over this area showed an indefinite shadow, but this was not as large as the area of retinal involvement. The defect in the visual field corresponded to the area of retinal separation.

It was the impression of one of us (C. I. T.) that the patient had a malignant melanoma of the choroid, and consultation with several colleagues confirmed this opinion.

The patient entered the hospital on Dec. 1, 1950, for study with radioactive phosphorus; the test was carried out on the following day. The count on the normal eye was 270 per minute, and

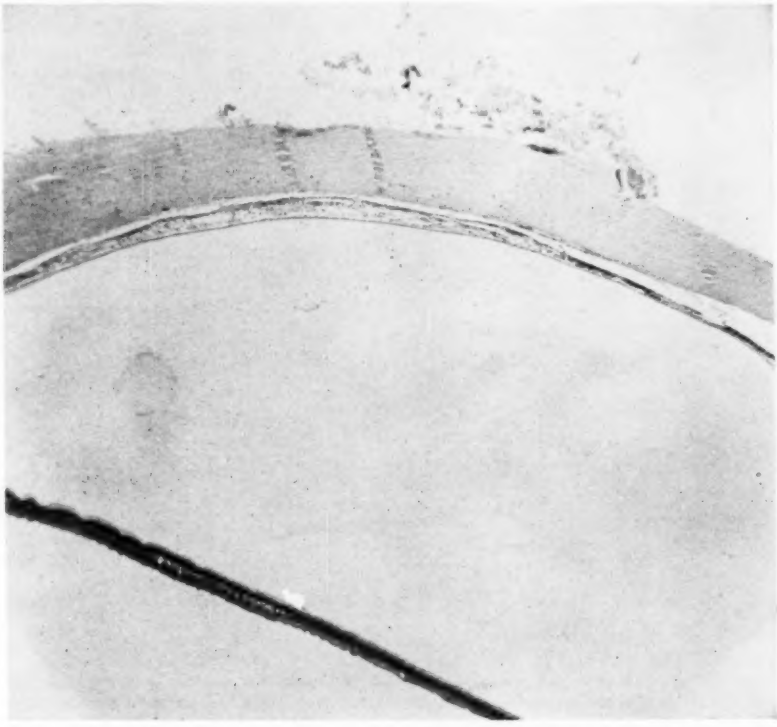

Fig. 3 (Case 1).—Photomicrograph (× 15) of section through the eye at the site of the retinal separation.

that over the suspected tumor of the right eye was 265, as were similar counts over the other three quadrants. This result failed, of course, to indicate the presence of a tumor. Despite the negative result of the test, however, the clinical evidence pointed so strongly toward a tumor as the cause of the detachment that enucleation of the right eye was done on Dec. 4. However, gross and microscopic examinations revealed no evidence of intraocular tumor (Fig. 3). In vitro counts on tissue of the sclera, retina, and choroid were all near the same figure of 400 per minute per gram.

Case 2.—A woman, aged 45, had had disturbed vision in the left eye for two weeks. Vision in this eye measured 20/20 (Snellen), and external examination revealed no abnormality. Slit-lamp examination with the biomicroscope also showed a normal condition. Ophthalmoscopic

examination revealed a large area of detached retina in the nasal half; this appeared as a solid detachment in that there was evidence of pigmentation and the borders of elevation were fairly abrupt. No retinal tear was found. Transillumination revealed a shadow when the light was in the area of the sclera overlying the detachment. The visual field showed a large scotoma corresponding to the area of separation.

The radioactive-phosphorus test was administered on Feb. 12, 1951. Over the area of the suspected tumor the count was 1,150 per minute, while in the opposite (temporal) region of the sclera the count was 500. The repeated count, one hour after injection of the isotope, gave similar results.

On the basis of the ophthalmologic findings and the radioactive-phosphorus studies, a diagnosis of melanoma of the choroid of the left eye was made. Enucleation was carried out, and gross

Fig. 4 (Case 2).—Photomicrograph (× 15), of section of the eye at the site of the tumor, showing retinal separation owing to melanosarcoma.

and microscopic examinations revealed melanosarcoma of the choroid (Fig. 4). Figure 5 shows the radioautograph made on a section of the eye.

Counts on the fresh specimens were as follows: The counts per minute per gram on the tumor tissues were 50,000; on a section containing tumor and sclera, 15,950; on three different sections of sclera, 8,900, 8,520, and 7,200, respectively.

Case 3.—A man, aged 55, presented himself on April 30, 1951, because of loss of vision in the right eye. Examination disclosed that the uncorrected vision in this eye was 20/30. External examination revealed essentially no abnormality. Ophthalmoscopic examination showed a darkly pigmented elevation of the retina, beginning adjacent to the ciliary body and extending posteriorly almost to the macula. This elevation was well demarcated, with sharp borders. The

intraocular tension was 18 mm. Hg (Schiøtz). Transillumination of the eye showed a definite shadow when the light was placed over this area on the sclera.

Radioactive-phosphorus studies were made, with the counts taken one-half and one hour after injection. Over the area of the suspected tumor, a count of 850 per minute was obtained at the peak, which was one hour after injection. In the opposite (nasal) half of the eye, behind

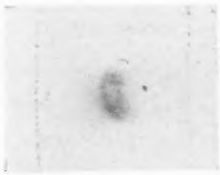

Fig. 5 (Case 2).—Radioautograph of sectioned eye.

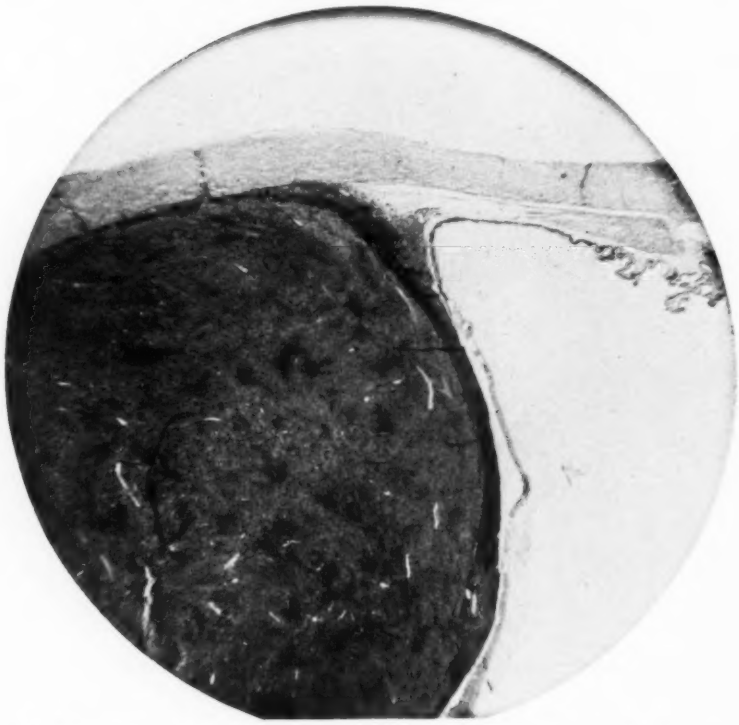

Fig. 6 (Case 4).—Photomicrograph (× 15) of section of the eye at the site of the tumor, showing retinal separation owing to melanosarcoma (courtesy of Dr. Gerald T. Schwarz).

the limbus, the count was 510 per minute. These findings showed an increase in uptake of radioactive material in the area of tumor, furnishing confirmation of the clinical diagnosis of malignant tumor.

After enucleation of the eye, on the following day, gross and microscopic examinations revealed the presence of malignant melanoma of the choroid. Counts on the fresh specimen

showed 1,965 per minute per gram for the tumor, 420 for the sclera from the opposite half of the eye, and 533 for the sclera adjacent to the tumor.

CASE 4.—A man, aged 35, had noticed failing vision in the left eye for two weeks. Examination revealed that vision in this eye was 20/25, uncorrected. External examination of the eye showed essentially a normal condition. Biomicroscopy revealed a normal anterior segment. By extending the slit-lamp beam into the vitreous diagonally, and with the biomicroscope, a dark-brown, pigmented mass, extending into the vitreous from just behind the ciliary body, could be observed. Ophthalmoscopic examination showed a few loose strands in the vitreous. A large rounded elevation of the retina was seen; this arose just behind the ciliary body and extended posteriorly halfway to the nerve head. This tumor was deeply pigmented and had sharp elevated borders. Transillumination of the left eye showed a shadow in the region of this tumor.

The radioactive-phosphorus studies were made on July 31, 1951. Over the tumor, the counts after ½ hour, 1 hour and 1½ hours were 430, 518 and 440 per minute, respectively, thus reaching a peak at the one-hour interval. The counts in the other quadrants of the left eye corresponded to the counts in the normal (right) eye, which were all approximately 200 to 225 per minute. This definite increase in uptake of the radioactive material further substantiated the diagnosis of intraocular malignant tumor.

Enucleation was not done in this case until Aug. 24, at which time gross and microscopic examination showed the presence of a malignant melanoma of the choroid. On the day before operation, another injection of 500 mc. of radioactive phosphorus was administered. The counts on the fresh specimens were as follows: tumor, 2,100 per minute; sclera distant from the tumor,

Fig. 7 (Case 4).—Radioautograph of sectioned eye.

602; retina, 715. A section of the eye through the tumor and a radioautograph are shown in Figures 6 and 7, respectively.

CASE 5.—A woman, aged 30, complained of blurred vision in the left eye. External examination revealed no abnormality. Vision was 20/100. Slit-lamp microscopy revealed that the anterior segment was normal. Ophthalmoscopic examination disclosed a large, darkly pigmented elevation of the retina in the upper temporal quadrant, extending downward to the region of the macula. The borders of this elevation were definite. The fundus was otherwise normal, as was the intraocular tension. Transillumination showed a shadow in the region of this elevation.

At 40 minutes after injection the peak over the site of the tumor was reached, being 1,622 per minute, as compared with 1,046 over the sclera of the normal (right) eye. At the end of 1 hour 20 minutes the count had begun to diminish to 1,362 per minute over the tumor and 867 over the normal sclera. From then on, the counts began to level off somewhat, so that 24 hours later the count over the tumor was 515 and that over the normal sclera was 422 per minute.

Enucleation was then carried out, and fresh specimens showed a count of 1,055 per minute per gram for the tumor tissue and 216 for sclera adjacent to the tumor. Gross and microscopic examination of this eye revealed the presence of melanosarcoma of the choroid.

CASE 6.—A woman, aged 42, had had a radical mastectomy for carcinoma of the right breast six months before she came, on Aug. 1, 1951, for ophthalmologic examination because of failure in vision of the right eye. External examination and slit-lamp microscopy revealed no abnormalities. Ophthalmoscopic examination showed a yellow-white, elevated area in the lower temporal quadrant of the retina. The elevation was gradual and diffuse, and not definitely pronounced, but it had a "solid" appearance. Clinically, the fundus lesion had the appearance characteristic of a

metastatic carcinoma. On transillumination, there was a shadow over this area of detachment. No operation was performed in this case.

The radioactive-phosphorus test was carried out on Sept. 25, 1951. Over the tumor of the right eye the counts obtained were 2,552 per minute, as compared with 2,040 over the sclera of the left eye. Two hours later, the reading over the tumor was 854 counts per minute, and that over the normal sclera, 560 per minute.

CASE 7.—A man, aged 60, complained that vision in the right eye had been disturbed for three days. The visual difficulty involved the nasal half of the visual field. The left eye had been removed years before because of a penetrating wound. Vision in the right eye measured 20/100 (Snellen). No abnormalities were evident on external examination. Slit-lamp microscopy revealed some haziness of the lens nucleus. Ophthalmoscopic examination showed a large area of retinal separation, involving the temporal half, between the ora serrata and the macular region. A horseshoe-shaped tear was evident in the upper temporal quadrant. Transillumination of the eye failed to reveal a shadow.

Even though the evidence was conclusive that in this case the retinal separation was due to fluid and retinal laceration, radioactive-phosphorus studies were carried out for control purposes.

Counts with Radioactive Phosphorus

	In Vivo (Maximal Counts per Minute)		In Vitro * (Counts per Gram per Minute)	
Case	Normal Eye	Over Area of Retinal Separation	Nontumor Tissue	Tumor Tissue
1	270	265	Sclera 400 Choroid 390	.....
2	500	1,150	Sclera and tumor 15,960 Sclera 8,900	50,000
3	510	850	Sclera near tumor 583 Sclera opposite tumor 420	1,965
4	225	518	Sclera 602 Retina 715	2,100
5	1,046	1,022	Sclera 216	1,055
6	2,040	2,552	.....	.....
7	....	701-755 (All quadrants)	.....	.....
8	270	327-334 (All quadrants)	.....	.....

* All in vitro specimens, with the exception of those in case 3, were run through a fixative prior to counting.

The counts made at varying intervals after the injection of the 500-mc. dose of radioactive phosphorus showed similar figures for all quadrants of the right eye, as was expected. In all quadrants of the right eye the count was 701 to 755 per minute.

These negative findings confirmed the clinical impression. This patient subsequently underwent operation for retinal detachment.

CASE 8.—A man had been treated three years earlier for secondary glaucoma, at which time an iridectomy was performed. Later, he had been treated for active uveitis with secondary glaucoma, and another iridectomy was done. The eye remained quiet for six months, and then hypertension developed, owing to changes in the angle of the anterior chamber (as seen with gonioscopy) and swelling of the lens. At this time, a large, darkly pigmented iris cyst appeared in the anterior chamber, situated at 12 o'clock, at the site of the first iridectomy.

Although the cyst in the anterior chamber could be transilluminated, and hence a malignant growth was not strongly suspected, this case presented a problem in which the use of a radioactive isotope could yield valuable diagnostic information in eliminating the possibility of a new growth.

The radioactive-phosphorus test was performed on Aug. 14, 1951. Counting was begun five minutes after injection, and repeated at 15-minute and ½-hour intervals. Over the sclera of the normal left eye, the counts ranged from 167 to 270 per minute. All quadrants of the right eye showed higher, but similar, counts, of between 327 and 334 per minute.

Since the count was no higher in any one area of the affected eye, the clinical impression that malignant tumor seemed unlikely was confirmed.

COMMENT

The foregoing cases suggest that the use of the procedures described for determination of uptake of P^{32} in ocular tumors may be extremely valuable in determining the nature of a retinal separation, i. e., whether the separation is caused by fluid or by a choroidal tumor. Most detachments which result from fluid pressure show a retinal tear, under careful examination, but in some instances no laceration is evident. In these questionable cases and in those in which the detachment may be due to hemorrhage following trauma, the diagnostic ability of the ophthalmologist may be taxed to the utmost.

In a case of separated retina in which the cause is obvious, as is true when the tear is visible or the separation follows injury, investigation with radioactive material is not indicated (Case 7). However, if the detachment is of questionable origin, especially when no tear in the retina is discernible, even though the surgeon may feel doubtful as to whether or not a tumor is present, measurements with radioactive-phosphorus may be very helpful, and perhaps even decisive, in making the diagnosis.

Case 1 reveals the importance of this test as an aid in determining the cause of a separated retina. The patient had a large area of separated retina, but no tear was visible; however, the clinical appearance suggested the presence of melanosarcoma. Consultation with several colleagues in ophthalmology confirmed the impression of one of us (C. I. T.) that the case was one of choroidal tumor, and the transillumination test was indecisive. The radioactive-phosphorus test failed to show any increase in emission of beta radiation over the site of the suspected tumor. At the time this test was made (the first in the series), we had no experience with other cases to help in the interpretation and evaluation of this result. Therefore, on the basis of the clinical diagnosis, the eye was enucleated. Histologic study, however, confirmed the results of the radioactive-phosphorus test, for there was no evidence of tumor tissue. In view of our later experience, such negative findings in the radioactive-phosphorus test would be given greater weight in the decision regarding operative treatment in any case of this type.

In all the other cases in which a tumor was suspected, a malignant lesion was indicated by the differential uptake of P^{32}. In these cases the result was confirmed by operation and histologic study except in the instance of suspected metastatic carcinoma (Case 6).

In Case 8 the presence of a cyst in an infected eye presented a problem on which the use of radioactive phosphorus could yield interesting diagnostic information. Although the counts were increased in this eye, as compared with those for the normal eye, there was no one area (as in the cases of tumor we have observed) in which the count was higher than in other parts of the affected eye. The elevation of the count in the diseased eye strongly indicated the possibility that the increased vascularization of the whole uveal tract caused the generalized increase in uptake of the radioactive substance. This problem of P^{32} uptake in inflammatory conditions is being subjected to further investigation.

In all the cases we have studied the lesions were situated in the anterior portion of the choroid, so that they were readily accessible for counting. This, of course,

simplified the technique, but tumors situated more posteriorly could still be measured for uptake of radioactive phosphorus by rotation and fixation of the eye. The special probe which we are designing should be capable of reaching posterior choroidal tumors.

SUMMARY

With recognition of the importance of localization of brain tumors by means of radioactive isotopes, we have applied this principle to similar localization of intraocular tumors as a diagnostic test in questionable cases presenting retinal detachment.

The method of localization is outlined, along with the technique of determinations of radioactivity in vivo and in vitro. Radioautographs are used to illustrate photographically the concentration of radioactive material.

The case histories reported include two in which the results of the test were negative, thus demonstrating the importance of this test in the evaluation of the cause of retinal separation. These studies, which must as yet be considered preliminary, thus provide strongly presumptive evidence that the identification of intraocular tumors may be enhanced by the use of P^{32}.

Dr. H. L. Friedell, Professor of Radiology, made helpful suggestions during the course of this study.

STELLATE-GANGLION BLOCK IN RETINITIS PIGMENTOSA

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AND
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CLEVELAND

FOR SOME time the value of cervical sympathectomy and cervical sympathetic block in the treatment of retinitis pigmentosa has been disputed. The beneficial results have been inconclusive, and the question has been raised as to whether the benefits derived from such measures are psychologic or organic.

For the purpose of evaluating the use of cervical sympathetic block in retinitis pigmentosa, we subjected a group of patients to cervical sympathetic block, first using procaine hydrochloride, and later we repeated the procedure using saline solution instead of procaine.

ANATOMIC BASIS OF SYMPATHETIC SURGERY

The preganglionic fibers arise from the intermediolateral tract of the gray matter of the spinal cord in the ciliospinal center of Budge. They concentrate in the stellate ganglion (a fusion of the inferior cervical and the first thoracic ganglion) and pass through the middle to the superior cervical ganglion.

The majority of fibers travel with the carotid artery, breaking up into a plexus along the internal carotid artery and a cavernous plexus along the artery in the cavernous sinus. A few fibers form a plexus along the vertebral artery, passing to the circle of Willis. As can be seen from Figure 1, sympathectomy of the superior cervical ganglion probably does not completely destroy the sympathetic innervation of the eye, although this is debatable.

TECHNIQUE

The technique which we used in cervical sympathetic block is the one described by de Sousa Pereira.[1]

In this procedure, it is not necessary to introduce the procaine low enough to block the stellate ganglion directly. As the patient lies on his back with his head turned to the opposite side, the lateral process of the fifth cervical vertebra is palpated. By means of pressure with the finger, the structures in the carotid sheath are displaced medially, and a 23-gage hypodermic needle, 1 to 1½ in. (2.5 to 3.8 cm.) in length, is introduced through the skin until its point

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From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

Preliminary report read before the Second Annual Wills Hospital Conference, Philadelphia, May 18, 1950.

1. de Sousa Pereira, A.: Blocking of Middle Cervical and Stellate Ganglions with Descending Infiltration Anesthesia: Technic Accidents and Therapeutic Indications, Arch. Surg. **50**:152 (March) 1945.

encounters the anterior surface of the lateral process of the fifth cervical vertebra (Fig. 2). Ten cubic centimeters of 1% procaine hydrochloride is then introduced; as a rule, a Horner syndrome appears within two or three minutes. The first indication is a slight increase in the amount of tears in the conjunctival sac. This is followed by narrowing of the pupil, narrowing

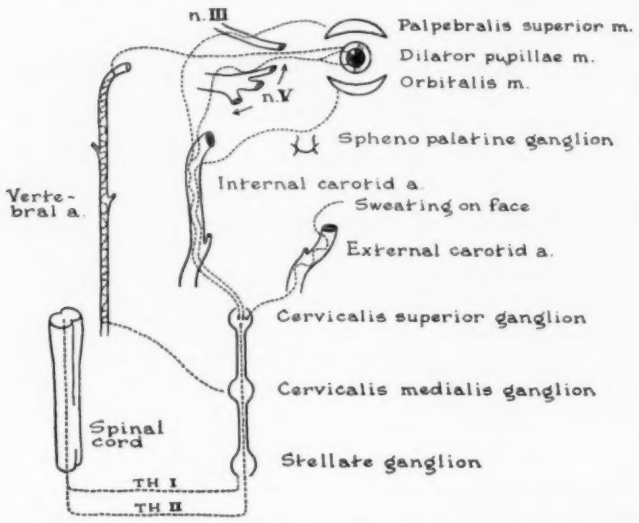

Fig. 1.—Sympathetic innervation of the eye. A majority of sympathetic fibers travel to the eye via the superior cervical ganglion and the carotid and cavernous plexuses; a few fibers to the eye pass via the plexus on the vertebral artery and the basilar arteries.

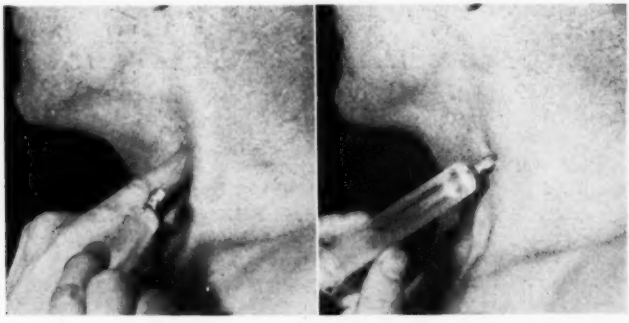

Fig. 2.—Area and technique of injection.

of the fissure, flushing of the sclera, and, in many cases, swelling of the nasal mucosa on the affected side. The most frequent side-reaction is a slight feeling of unsteadiness when the patient stands. Transient hoarseness due to paralysis of the vocal cords has been encountered on an average of not oftener than once in 200 cases. The Horner syndrome generally lasts from 30 minutes to an hour.

RESULTS

Of 14 patients upon whom this procedure was used, 7 claimed definite subjective improvement in vision; several of these patients were persistent in their claims.

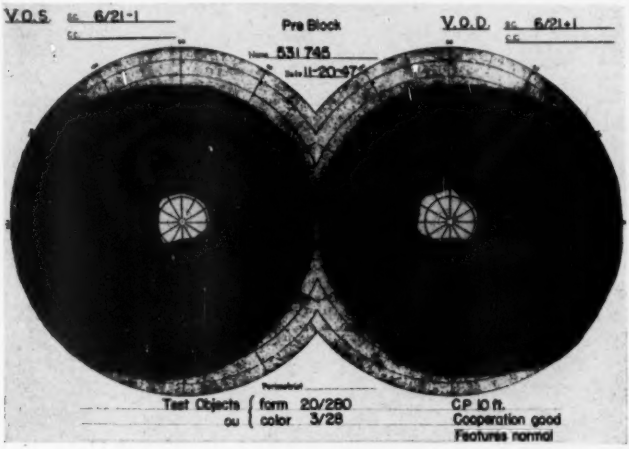

Fig. 3 (Case 1).—Visual fields before stellate-ganglion block.

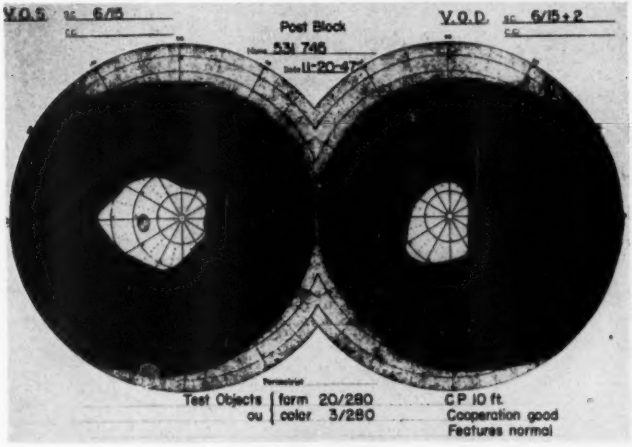

Fig. 4 (Case 1).—Visual fields after bilateral stellate-ganglion block.

Seven patients had no definite subjective improvement. Of the seven experiencing definite subjective improvement, three had cervical ganglionectomies. Although these three believed that they were subjectively improved after operation, each maintained the same visual field as before.

REPORT OF CASES

CASE 1.—A white man aged 36 entered the Cleveland Clinic with the chief complaints of night blindness and poor side vision. Nine years previously he had noticed gradually diminishing night vision and side vision. In the past three years this impairment seemed to have progressed

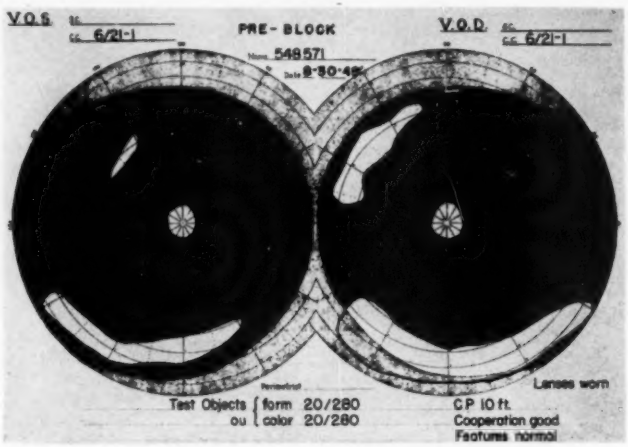

Fig. 5 (Case 2).—Visual fields before stellate-ganglion block.

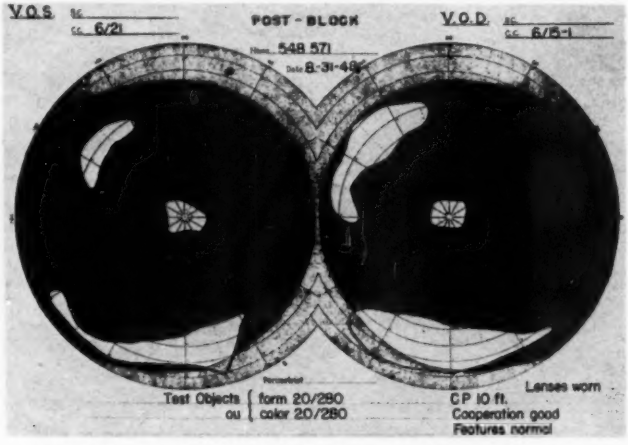

Fig. 6 (Case 2).—Visual fields after bilateral stellate-ganglion block.

rapidly. The past history was noncontributory. The family history disclosed that a brother who died of liver trouble had experienced similar difficulty with his eyes. Physical examination showed an essentially normal condition. Ocular examination revealed vision of 6/21 in the right eye and 6/21 in the left eye. Examination of the right eye showed a posterior star- haped opacity of the lens, a few vitreous floaters, no atrophy of the disk, severe generalized constriction

of the vascular tree, and, in the retina, pronounced pigment of bone-corpuscle shape about the periphery, with a clear macula. The left eye was essentially similar.

The patient was given bilateral stellate-ganglion block, with good ptosis. No change was evident in the caliber of the retinal vessels at the time of block. Vision immediately after block was 6/15 +2 in the right eye and 6/15 in the left eye (Fig. 3).

The patient showed questionable improvement in his visual fields and visual acuity (Fig. 4).

CASE 2.—A white man aged 52 came to the Clinic complaining of night blindness and poor side vision. For eight years he had been aware of gradually diminishing night vision. The family history disclosed that one brother, one sister, and two cousins had experienced the same condition. The results of physical examination were satisfactory. Ocular examination showed vision of 6/21 —1 in each eye. Examination of the fundus showed optic atrophy in both eyes, generalized vascular attenuation, and definite peripheral pigmentary deposits (Fig. 5). The patient was given bilateral stellate-ganglion block. Vision immediately after block was 6/15 —1 in the right eye and 6/21 in the left eye (Fig. 6). The patient observed definite subjective improvement. A bilateral cervical sympathectomy was done. Vision was then 6/21 in each eye. Examination of the fundus showed the same condition as before block. The patient experienced definite subjective improvement.

Nine of the original 14 patients who were given procaine cervical sympathetic block were recalled and subjected to the same cervical-block procedure except that saline was used instead of procaine. The results were as follows:

Six patients maintained that they had definite subjective improvement; three claimed no improvement. In no case was there definite improvement in visual fields or visual acuity after injection of the cervical sympathetic chain with the saline solutions.

Procaine block of the cervical sympathetic chain showed subjective improvement in 7 of 14 patients. There was no definite improvement in visual fields or visual acuity.

Saline injection into the cervical sympathetic chain, using the same technique as that with procaine block, resulted in subjective improvement in six of nine patients. None of these patients showed any definite improvement in the visual fields or visual acuity.

SUMMARY AND CONCLUSIONS

No actual objective improvement was shown in any of the patients who had cervical sympathetic block with either saline or procaine solution.

The subjective improvement following procaine injection was reported to be the same as that following saline injection.

From this series of cases it is concluded that the benefits derived from cervical sympathetic block are purely psychical.

We believe that stellate ganglionectomy is of no value in the treatment of retinitis pigmentosa.

THE VERTICAL COMPONENT IN STRABISMUS

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A CONSIDERATION of the vertical component in strabismus involves a study of those complicated cases in which a vertical deviation is associated with a horizontal deviation. The complex manifestations of these cases present a special problem, and the difficulties arising from improper management can be very great, both to the patient and to the physician. Nowhere is experience more necessary than in the diagnosis and treatment of this condition.

As our knowledge of oculomotor defects has increased, we are more and more impressed with the important role of vertical defects in strabismus, especially those involving the oblique muscles. It is increasingly evident that a vertical defect in heterotropia is an important motor obstacle to binocular coordination; when associated with a horizontal deviation, it is frequently the true underlying imbalance, the horizontal deviation actually being a secondary phenomenon.

Lack of proper consideration of the vertical deviation has frequently resulted in disappointing therapeutic results. Operation on the horizontal muscles, in the presence of an unrecognized vertical component, results in cosmetic improvement alone, almost never in the functional improvement which is the goal of surgery. Not only this, but even a good cosmetic result in cases of lateral deviations is frequently lost because of an unrecognized vertical component. White,[1] in discussing the operative failures of many excellent surgeons, stated that, almost without exception, a vertical imbalance was present. Scobee[2] stated:

> It has been my opportunity to see a number of patients with presumably only lateral deviations who have had from three to seven operations—all unsuccessful—on the horizontal muscles only. In every case there was a definite vertical component. The vertical-muscle surgery was done, and then one final procedure on the lateral muscles, and the results were good. I am certain that these unfortunate patients could have been saved several operations if the vertical component had been recognized.

Experience seems to indicate that a person with horizontal strabismus should not be operated on or otherwise treated without a thorough study and analysis of the vertical component, and that rules for the correction of a horizontal deviation are not the same in the presence of a vertical component.

PHYSIOLOGY OF VERTICAL BALANCE

Anatomical and physiological evidence points to a factor of stability in vertical-muscle balance. Although this stability is based on few positive data, its existence seems essential to the intricate functions necessary in efficient binocular action.

1. White, J. W.: Tr. Am. Ophth. Soc. **40**:118-126, 1942.
2. Scobee, R. G.: Personal communication to the author.

Certain data are suggestive. This stability of the vertical muscles is present at birth; the newborn possesses the power of conjugating the eyes in vertical movements. In contrast, horizontal movements are poorly conjugated at birth and require months before becoming stabilized. Indeed, full stabilization usually does not occur for several years, and even then the horizontal movements retain a variability which permits a wide range of flexibility and may under unfavorable conditions easily lead to instability.

Stability of the vertical balance is essential to efficient binocular action. Whereas the actions of the horizontal muscles are comparatively simple, the coordinated actions of the vertical muscles are highly complex, owing to the variable actions depending upon the direction of gaze. Because the axes of rotation of the vertical muscles lie outside Listing's plane, vertical movements call for a higher degree of coordination, in order that ocular movements may take place around an axis lying in the correct plane. The action of the vertical muscles must be balanced so that the various components are synchronized. For example, when the eye is turned up or down, the components acting around the vertical and anteroposterior axes are neutralized, leaving those which act around the horizontal axis combined in the correct proportions and thus permitting a movement free from unnecessary deviations.

The arrangement of the four vertical muscles represents the most economical way in which to achieve both a vertical movement free of torsion, following Listing's law, and a torsion of the eyeball where this is needed.

The integration of the various types of muscle action (vertical, horizontal, and torsional) which is present in varying degrees as the gaze is shifted from place to place necessitates a stable mechanism. Such a stability in the vertical balance allows the horizontal balance the flexibility essential for accommodation and convergence.

Although positive data are lacking, the stability of the vertical balance is seemingly brought about chiefly by two factors: the peripheral and the central mechanism. Because the eyes are in a common horizontal plane, and because of the peculiar anatomical arrangement of the muscles in relation to the globe, the type of insertions, and the specialization of the fascial membranes, which produce a check action on the muscles, a high degree of stability is present in the peripheral mechanism. This fact is evidenced by the comparatively small deviation found in the vertical imbalances as compared with the horizontal, as well as by the small amount of surgical correction required to produce the necessary result.

Evidence likewise points to a well-established, highly developed central mechanism, accounting to a great degree for the stability of the vertical balance and the remarkable capacity for adjustments essential to binocular vision. The coordinating mechanism in ocular movements depends not only on gross muscular contractions and relaxations but also on finely integrated neuromuscular actions (fusional movements), under the control of the higher centers. Such a mechanism must exert a restraining influence, in which variations in position are limited in order to achieve smooth binocular action in the various fields of gaze. This stable vertical balance seems essential in the binocular act, permitting the horizontal component to retain the high degree of latitude necessary to accommodation and convergence.

It is generally accepted that the range of vertical fusion—actually vertical vergence—is small. Comparatively limited fusion amplitude indicates the limited latitude of adjustability. In view of this limited range, vertical-fusion powers must be very strong in order to accomplish what they do.

According to Lancaster,[3] vertical vergence plays a minor role in binocular activity as compared with horizontal vergence. The various binocular adjustments made at different distances call for a minimum effort of the vertical-vergence function; vertical movements (up and down) are conjugate, and disjunctive movements are not called for except to correct minor deviations. The amplitude of horizontal adjustment is considerably greater. Every change in distance requires a change in horizontal vergence, and therefore a disjunctive adjustment. Horizontal movements are conjugate only when the distance of the fixation is not changed.

We have therefore in the vertical component a fixed relationship with a very limited range of reflex power of adjustment, while the horizontal component is endowed with great power of adjustability.

It is only natural that the horizontal balance, which is called on so frequently to make adjustments, should be highly flexible and that the vertical balance, which has little need for variability in ordinary daily use, should be very stable. Here is another example of the neuromuscular mechanism making adjustments according to demand.

FREQUENCY

Combined vertical and horizontal imbalance is found to be a fairly common occurrence, if data are analyzed carefully. White and Brown [4] stated that of 1,955 cases of motor anomalies, a vertical imbalance was exhibited in 36.6%. Bielschowsky [5] found that 45% of horizontal deviations were complicated by a vertical imbalance. Of 402 cases of combined vertical and horizontal imbalance reported by Anderson,[6] a vertical imbalance was shown in 286.

In Scobee's [7] series of 457 patients with esotropia, 195 (43%) had paresis of one or more of the vertically acting muscles. The incidence of the vertical component was 49% in the group with nonaccommodative squint, 45% in the group with partly accommodative squint, and 21% in the group with purely accommodative squint. (These statistics do not include cases of the minor vertical imbalance; if these were included, the percentage would be appreciably higher.)

ETIOLOGY

Because of the complex nature of the subject, a complete discussion of the various etiological factors in combined muscle defects will not be attempted; instead, only a brief consideration of those factors that may be regarded as important to the specific subject under discussion will be attempted.

A review of available data indicates that our knowledge of the etiology of combined deviations is based largely on supposition; in only a few instances, such as trauma, can we be positive. Anderson's [6] findings emphasize this point:

3. Lancaster, W.: Personal communication to the author.
4. White, J. W., and Brown, H. W.: Arch. Ophth. **21**:999-1009 (June) 1939.
5. Bielschowsky, A.: Arch. Ophth. **13**:33-59 (Jan.) 1935.
6. Anderson, J. R.: Brit. J. Ophth., Monograph Supp., No. 12, 1947.
7. Scobee, R. G.: Personal communication to the author.

In an analysis of 402 cases from an etiological standpoint, he was able to determine the cause of the deviation with certainty in only 10 cases, in all of which trauma was responsible.

As in other types of heterotropia, vertical deviations may develop as the result of a combination of several factors, although in most cases causative factors remain obscure. The commoner factors may be classified as follows:

1. Anatomical factors, such as the shape of the orbit; the size and shape of the eye; the volume and quality of the retrobulbar tissue; the functioning of the eye muscles, as determined by their insertion, length, elasticity, and structure, and the anatomical arrangement and condition of the fascia and ligaments of the orbit.

2. Paresis (toxic, traumatic, or congenital in nature).

3. Accommodative or refractive defects.

4. Disturbance of binocular unity, such as those resulting from corneal scars, cataract, vitreous opacities, retinal lesions, and lesions in the visual pathways of one or both eyes.

5. Innervational factors, i. e., psychogenic, fusional impulses, and the convergence impulse coupled with accommodation.

Various data suggest that vertical disturbances are a cause of horizontal deviations in many instances but that horizontal defects seldom cause vertical disturbances. This is because faulty vertical function is an outstanding motor obstacle.

A proper relation between the static angle and the fusion mechanism is essential; when disproportion exists, the squint becomes manifest. This disproportion may be due either to the static angle being too large to be overcome by a normal fusion mechanism or to the fusion mechanism being subnormal in development or injured by toxic or traumatic agents.

It is my impression that certain vertical-muscle imbalances are due basically to a disturbance of the peripheral mechanism (basal nucleus, peripheral nerves, and orbital structures). In most of these the causative factor is a mechanical defect resulting from a faulty anatomical relationship, i. e., malformation involving the orbit and orbital contents (extrinsic muscles, eyeball, fascial maldevelopments, etc.). Some are probably minor anomalies particularly associated with variations in the fascial sheath or in the tendinous insertion of the muscle. This opinion is based on observation in the operating room and in the dissecting laboratory, where such maldevelopment has been encountered. Although such evidence is not conclusive and does not permit a statement as to the frequency of such occurrences, it does suggest that many unexplained vertical defects are not due solely to the innervational factor. Such an anomalous condition of a vertical muscle will cause the muscle to underact, and the findings at examination may simulate a paresis of the muscle. If the effect of an anomaly is slight, the result is only heterophoria. If the effect of an anomaly is greater, the tendency toward heterotropia results; some other factor—accommodative or innervational—may increase the heterotropia.

It is therefore apparent that our concept of the causative factors at the basis of vertical defects is mostly supposition. Until more accurate data are compiled and greater refinement in our diagnostic methods is achieved, our knowledge of the etiological factors in vertical strabismus will continue to remain incomplete. Even with the most refined methods of investigation, certain factors may remain obscure.

DIAGNOSIS

The analysis of a combined vertical and horizontal defect is frequently a complex problem, and many unusual cases tax our present knowledge. The problems of convergence and divergence anomalies are fairly well understood, but as yet no such clear-cut criteria have been established for defects of the vertically acting muscles. The action of the vertical muscles is much more complex than that of the horizontal rectus muscles; consequently, a defect in a vertically acting muscle does not lend itself to the same degree of differentiation as does a defect in a horizontally acting rectus muscle.

The horizontal defect is more concomitant, and the findings are more uniform; the vertical defect presents a variable symptom complex because the amount of disturbance varies with the degree of involvement, the direction of gaze, and whether the patient fixes with the normal or with the affected eye.

The diagnosis is further complicated by the development in the vertical anomalies of secondary contractures in the contralateral associated muscle and in the homolateral direct antagonist, resulting in disturbances of all the torsional, vertical, and horizontal movements in which the affected muscle normally takes part.

The diagnosis of combined vertical and horizontal deviations involves primarily a consideration of the vertical component. The presence of a horizontal component complicates the diagnosis of a vertical defect according to its degree of severity. Horizontal deviation usually develops in the eye with the greater refractive error, along with sensory inhibition and amblyopia; the vertical deviation may be found in either of the two eyes.

Principles Governing Diagnosis of Vertical Deviations.—Principal Action of the Muscle: The principal action of a vertical muscle varies with the direction of gaze. It is incorrect to assign a principal action to a vertical muscle, because the importance of a given action varies with the position of the globe. For example, the depressing action of the superior oblique is greatest when the eye is adducted and gradually diminishes in importance as the eye is abducted. In the abducted position the principal action of the muscle is torsion, which action gradually diminishes as the eye is adducted.

Postural Attitude: This is a factor of importance in the diagnosis of vertical defects. The response on the part of the body to an underacting ocular muscle is to compensate as far as possible for the disturbing effects of the diplopia. This can be accomplished by either suppressing the image of one eye or holding the head in such a position that the diplopia is abolished or lessened. The patient tends to assume a postural attitude in which the underacting muscle is sufficiently relieved of its function that binocular vision is possible.

Fixating Eye: Determination of the fixating eye is fundamental in the diagnosis of vertical-muscle defects. In all cases of underaction of sufficient severity to break up binocular vision, the eyes become dissociated; and whether the affected or the normal eye is habitually used for fixation must be considered.

According to Scobee,[8] vertical deviations due to the oblique muscles will be exaggerated in esotropia and masked in exotropia if the nonfixing eye is the affected

8. Scobee, R. G.: The Oculorotary Muscles, St. Louis, C. V. Mosby Company, 1947, pp. 68-77.

one, and exaggerated in exotropia and masked in esotropia if the fixing eye is the affected one. Experience indicates that the normal eye is not necessarily the fixating eye; other factors, such as the dominant eye, refractive error, and visual acuity, are apparently determining.

Stage of Development of a Muscle Defect: The adjustment to a vertical defect is dependent for the most part upon the time of onset of the squint, for the symptoms of a vertical noncomitant squint depend upon whether the binocular reflexes have been fully developed.

In congenital and infantile squint, the defect appears before the binocular reflexes have become established. At this time the reflexes are unformed or unstable, so that by the activity of inhibitions or the facilitation of abnormal reflexes an ordered pattern of behavior is built up which involves little conscious inconvenience.

Postural attitudes will usually be present unless one eye is amblyopic or unless the fusion faculty permits the deviation to be overcome without intervention of the head tilt. For tilting to be present, the patient must be able to achieve binocular single vision and have sufficiently good vision in each eye and adequate fusion to appreciate diplopia. The postural attitude to maintain binocular vision is adopted at about 18 months to 2 years of age, when fusion begins to develop. Its presence can almost be accepted as a diagnostic indication that the involvement is of early infantile origin, although it may develop in adulthood when vertical movements of the eyes are disturbed.

In cases of congenital and infantile squint, diplopia may be eliminated by the suppression of one image or the development of abnormal correspondence on looking in the direction of the underacting muscle.

The diagnosis of early stages of acquired squint in an adult presents no unusual difficulty. If the condition is both recent and pronounced in degree, the diagnosis is easily made, since in such instances the findings indicate clearly which is the affected muscle. Moderate underaction is more difficult to detect, and various procedures other than visual observation may be required, though usually little difficulty is presented by such cases if the squint is recent and only one muscle is involved. Diplopia is usually the most disturbing symptom in squints which develop after the binocular reflexes have become established, because suppression or amblyopia does not develop easily in an adult. Persons with nonconcomitant squint acquired in later life do not, as a rule, acquire compensatory postural attitudes, or only to a slight degree, as adults find it difficult to maintain the complicated postures of torticollis.

In later stages a more complex picture, with greater diagnostic problems, is encountered, and intensive investigation may be required to determine the nature of the original lesion. Over a period of time, certain changes occur which cause the defect to assume certain characteristics of a concomitant deviation. The vertical defects cannot become as concomitant as do the horizontal deviations, because vertical muscles have a variable action depending upon whether the eye is abducted or adducted; for example, the vertical action of a rectus muscle is greatest when the eye is abducted, and that of an oblique muscle, when the eye is adducted. In involvement of the superior oblique, a tendency to concomitance is not very evident, even when compensation by head tilting has been abandoned or has not developed.

One should remember, therefore, that the manifestations differ according to the duration of the involvement. If the underaction of the muscle is of recent origin, there is little difficulty in determining the affected muscle. In the intermediate stage, the picture may be somewhat confused if one overlooks a beginning contracture of the antagonist muscle or an overaction of the yoke muscle, or if the affected eye is the fixating eye. In the late stage, the affected muscle may be completely or partially recovered but contractures of the antagonist and yoke muscles remain. It is thus apparent that knowledge of the length of time the condition has existed is of inestimable help to the diagnostician.

Diagnostic Procedures Employed in Analysis of a Case.—The examiner has at his disposal a number of diagnostic procedures. Conditions such as the age of the patient, time of onset, causative factor, visual acuity, and degree of binocular action determine which tests should be employed and which should be omitted. The personal experience of the examiner is also an important factor in the selection of tests in a given case. Training and years of experience have made him particularly familiar with certain procedures, and he has become skilled in their technique and interpretation; other tests are reserved for the more complex cases requiring further confirmation.

Generally speaking, rules for the selection of tests may be summarized as follows:

Tests should be of an objective nature only in the very young child and in the older child or adult exhibiting definite amblyopia or marked suppression. The subjective tests are of value if the patient is mature enough to understand what is desired.

If suppression is not deep, amblyopia is not pronounced, and correspondence is normal, both objective and subjective tests may be performed, but the subjective tests should be considered supplementary procedures.

Both objective and subjective tests are used when the strabismus is of recent onset or when single binocular vision exists.

Diagnosis in the case is based for the most part on procedures which analyze three objective symptoms (abnormal deviation of the eyes, limitation or excess of movement, and the adoption of compensating postural attitudes) and two subjective symptoms (diplopia and false orientation).

MANAGEMENT

Because the vertical deviation is usually considered the primary defect, and the horizontal deviation secondary to it, emphasis will be given the vertical deviation in the following discussion.

The subject will be considered in two phases: (*a*) management of vertical deviations and (*b*) management of combined vertical and horizontal deviations.

A. Management of Vertical Deviations.—Briefly stated, the principles applicable to management of vertical deviations are as follows:

1. Correction of the deviation should be accomplished as early as possible in the life of the child. This is of paramount importance, for the following reasons:

(*a*) The torticollis, if present, is disfiguring and in time produces a spastic contracture of the muscles of neck, head, and trunk.

(*b*) A congenital or infantile paralysis changes its characteristics and becomes more complicated, owing to structural changes in the affected muscle, in its antagonist, and in the contralateral synergist.

(*c*) Suppression and amblyopia may occur if the patient is not treated early. Unless the child is treated while still in the developmental stage, a functional cure is difficult or impossible to obtain. Amblyopia which exists from birth does not as a rule respond to treatment; if higher visual acuity is present before amblyopia develops, it is possible to restore vision to the level at which inhibition or suppression started. Therefore, the extent of amblyopia and the amount of vision which can be reclaimed vary with the degree of visual development before inhibition, with the duration of the condition, and, to some extent, with the psychological habits of the patient. Early treatment permits parallelism of the eyes in some habitually employed direction of gaze, so that bimacular vision can be developed and abnormal binocular reflexes will not become fixed. Before this is accomplished, care should be taken to treat amblyopia, if it is present.

Children who possess binocular vision, although it may exist only in the compensatory position adopted by the head, should be operated on as soon as it is practicable. If binocular vision has not developed and if suppression or amblyopia has become fixed, the deformity can be corrected in many cases to give a cosmetic result.

(*d*) The deviated eye becomes a serious factor in the child's appearance; the psychological, social, and economic importance of such a condition cannot be overestimated.

2. In every case the refractive error must be determined and, if necessary, corrected. Further therapeutic procedures should be decided on only after the correction has been worn by the patient for a certain length of time. This routine makes it possible to establish the importance of the accommodative factor. Some patients may show no appreciable change, while in others both the horizontal and the vertical angle of squint are materially reduced by the wearing of glasses.

3. The use of vertical prisms may promote better binocular action when vertical deviation is of moderate degree and when a fairly large field of concomitance is present. If there is concomitance over a useful field, the patient may be rendered very comfortable with prisms which provide fusion in this area. Prisms may be effective in overcoming the mechanical handicap if the hypertropia is anatomical and static in nature. Prisms can usually be given up to a strength of 10 Δ before they cause distortion; this tendency is lessened when they are distributed between the two eyes. However, in most cases in which a high prism correction is required, surgery is indicated because of the obvious objections to wearing a high-prism correction.

Prisms in the form of a clip-on may be used as a diagnostic step in determining the effect on the horizontal component of neutralizing the vertical component. The examiner can thus obtain more positive evidence as to the relation of the two components. Experience has shown that in certain cases the tendency to a horizontal deviation may be appreciably lessened when the vertical component is neutralized.

Clip-on prisms may also be used to neutralize a residual vertical deviation after operation. If binocular action is improved after wearing the clip-on prism, the prism correction can be incorporated into the glass.

If a residual vertical deviation after operation is 2 to 3 Δ or over, it is best immediately to incorporate a prism correction into the new prescription for glasses. It has been my experience that, although the vertical component may not be entirely neutralized by the prism, a definite improvement in the binocular action frequently occurs.

As a rule, it is not advisable to incorporate more than 5 or 6 Δ into the permanent correction because of the weight added to the glass and the objectionable appearance. In these cases, surgical intervention may be considered if the vertical defect is an obstacle to binocular unity.

After the prescribing of the vertical prism, the patient should be checked periodically to determine its effect. After the prism has been worn for a time, the amount of deviation may lessen, requiring a reduction in prism strength; in other cases, greater vertical deviation may appear, necessitating a stronger correction. The prescription of a vertical prism must therefore be considered a temporary measure in certain cases, in which the aim is to determine the effect upon binocular action when the mechanical obstacle caused by the vertical deviation is lessened to a point at which binocular action is possible.

In certain cases the removal of the vertical mechanical obstacle by prisms has no appreciable influence on the binocular action, whereas in others a definite improvement is achieved. In the former, in which the improvement is negligible, no attempt is made to correct the vertical component; in the latter, the defect is neutralized either by prisms, if it is moderate in amount, or by operation, if it is high.

Subjective measurements on the amblyoscope have been found valuable not only in determining the initial vertical measurements but also in following the patient after prisms are prescribed, and thus in estimating the effect of the prism on the vertical defect.

4. Fusion training may increase the patient's ability to coordinate his eyes. Improvement by orthoptic training is not feasible unless the vertical deviation is moderate in degree; satisfactory single binocular vision with good working fusion can rarely be obtained as long as there is an appreciable vertical component.

When the vertical deviation has been lessened by the use of prisms, an attempt should be made to stimulate binocular action by fusion training. If neither wearing of prisms nor fusion training improves binocular action and an appreciable vertical deviation exists, an operation is indicated to reduce the amount of vertical deviation. After operation, prisms may be used to neutralize a residual vertical deviation, if present, and fusion training may be given further trial.

5. Surgical correction of the defect is indicated when other measures have proved inadequate, when the defect is causing sufficiently severe symptoms, or for cosmetic reasons.

(*a*) Operative treatment aims to secure a more physiological position of the eyes at rest, so that less mechanical adjustment is necessary on the part of the neuromuscular mechanism and the fusion faculty. The neuromuscular mechanism has a remarkable capacity for adjustment; indeed, in the presence of such flexi-

bility, some anatomical defects do not assume great significance. A surgical step may not by itself produce exact results, but with the aid of neuromuscular adjustability a satisfactory outcome can be achieved. Surgical correction of the vertical defect is accomplished, as a rule, by strengthening an underacting muscle by resection or tucking of the muscle or by weakening an overacting muscle by recession or tenotomy. As a general rule, resection or tucking of the underacting muscle is preferred to advancement, first, because of the relatively small amount of correction desired and, second, because the original insertion is used and torsion is less likely to result.

(*b*) Many operative patients fail to obtain relief, not because operation was contraindicated or was improperly performed, but because the wrong muscles were chosen for correction. This error can usually be avoided by careful analysis of the case. Because binocular vision exists in some cases, operative failures may greatly incapacitate the patient.

(*c*) Great care should be taken not to overcorrect a vertical defect. Because of the peculiar anatomical arrangement of the vertical muscles, vertical defects are usually very moderate in amount as compared with horizontal defects; also, a few millimeters of correction on a vertical muscle is much more effective in producing the desired result than is the same amount of surgical correction on a horizontal muscle. Overcorrection of a vertical defect may create an insurmountable mechanical obstacle to binocular vision because of the limited vertical-fusion amplitude.

(*d*) Surgical procedures are not limited to vertical defects of high degrees but can be used effectively in moderate defects. In fact, small amounts of vertical deviation lend themselves well to surgical correction.

(*e*) There is a definite tendency at present to operate on the offending muscle if it can be determined. Up to a few years ago, an attempt to correct a deviation caused by an oblique muscle was carried out on a vertical rectus muscle. Present data indicate that if an oblique muscle is the primary offender, it should receive primary consideration, although an operation on an oblique muscle may be combined with an operation on the vertical rectus muscles when operation on the oblique muscle only will not produce sufficient correction.

Evidence obtained from anatomical studies and clinical experience seems to point to conservatism in operating on the vertical rectus muscles. Various secondary effects may result from such surgery, i. e., variation in the position of the lids, limitation of movement, and torsional disturbances. When there is a choice, some surgeons prefer to operate on the inferior rectus muscle, because of the greater effect of superior-rectus surgery on the width of the lid fissure. However, operations on the inferior rectus may upset the balance in the lower field of fixation, which is much more important in daily use than is the upper field of fixation.

I approach surgical procedures on the rectus muscles with due consideration, and when an oblique muscle is primarily involved, I reserve operation on the vertical rectus muscle for a secondary step if necessary. In cases of more pronounced oblique-muscle involvement, a more liberal operation is performed on the affected oblique muscle, in conjunction with the surgical procedure on the associated vertical rectus muscle. It has been my experience that in cases of pronounced squint the inferior rectus can be resected as much as 5 mm. but should not be

recessed more than 3 mm. In the case of the superior rectus, a recession of more than 3 mm. is usually inadvisable because of the complex anatomic relations of the area, though a resection of as much as 5 mm. has proved satisfactory.

(*f*) It should be understood from the outset that in the great majority of cases ultimate correction cannot be expected from one operation. It is a mistake to plan the required surgical procedure for one sitting. No prediction can be made of the corrective value of each millimeter of recession or resection; a rule of thumb giving the number of degrees of correction for each millimeter of shortening or lengthening of a muscle is misleading. It is therefore important to instruct the parents before any surgical correction is attempted that more than one procedure may be necessary.

In general, in dealing with problems of vertical deviation, the surgeon should be content to produce an undercorrection, which may be amenable to further procedures, rather than to accomplish too much and find reconstruction difficult. He should also be willing to operate on the fellow eye when necessary, rather than try to correct a high degree of strabismus by an extensive operation on one eye.

(*g*) Surgical correction should be avoided, or used only with caution, when the error is essentially of nervous origin (as in the dissociated type). An operation on peripheral structures cannot correct a faulty innervation of central origin; a vertical deviation merely perpetuates itself at a different elevation. In these cases only the stable portion of the deviation, such as an esotropia, is corrected surgically.

(*h*) In acute paralyses the underlying cause should first be treated whenever possible. When the final outcome has been established, surgical correction should be considered. In paresis of traumatic origin, it is wise to consider the possibility of recovery without operation. Most patients, if they are going to recover, will do so by the end of the sixth month, but some require longer, one or even two years, for full recovery. It is a safe rule to consider the paresis stationary when it has shown no change for six months. Of his large series of patients, Bielschowsky [5] found that 38% recovered spontaneously.

(*i*) Diplopia is often a reason for surgical intervention; usually, however, operation is for the secondary symptoms the diplopia causes: head tilting, confusion, vertigo, and nausea. Although it is not always possible to abolish diplopia by operation, the deviation can be made more concomitant. This greater concomitance makes the patient less confused, and the remaining error may then be corrected by prisms.

Three points should be borne in mind in operation for correction of a diplopia:

1. A variable diplopia is much more annoying than one which remains approximately the same in all directions of gaze.

2. A diplopia in the lower fields is more productive of asthenopia than one confined to the upper fields. It is important to secure binocular vision in that part of the field of fixation which lies below the horizon and near the midline. It is not nearly so important to secure binocularity above the horizon or in the extreme horizontal positions.

3. The character of the diplopia must also be considered. Horizontal diplopia is easily overcome by turning the head into the field of action of the paralyzed muscle. Vertical diplopia can be overcome, but less easily, by elevating or depressing the chin. Torsional diplopia can be overcome only by tilting the head on the

shoulder. Torsional diplopia is by far the most annoying to the patient, as there are constant blurring and confusion of all objects. Torsional diplopia, if present, must therefore be eliminated if possible, and it should be taken into consideration in planning operative procedures, especially on the superior oblique. Any operation should be avoided which might either create torsional diplopia or make an existing one worse.

B. Combined Vertical and Horizontal Deviation.—Undercorrection or overcorrection in operations for horizontal defects is frequently due to lack of proper consideration of the vertical deviation. Rules for correction of a horizontal deviation are not the same in the presence of a vertical component. Because of this, a person with horizontal strabismus should not be operated on or otherwise treated without a thorough study and analysis of the vertical component.

Certain principles apply to the management of combined vertical and horizontal deviations.

1. When the deviation is both vertical and horizontal, the neutralization of the vertical error frequently allows the normal reflexes to deal with the horizontal error, so that prismatic correction of the vertical component may be effective in providing complete relief; conversely, an attempt to correct a horizontal deviation in the presence of an untreated vertical deviation will almost certainly result in failure. When correction of the vertical deviation by prism influences the lateral but little, the lateral deviation may be safely corrected first.

Therefore, operation on the horizontal muscles in mild cases should be carried out only after the vertical deviation has first been corrected by prisms; smaller degrees of horizontal deviation with a moderate amount of vertical deviation may disappear after correction of the vertical deviation with prisms, especially if the vertical error is corrected before the horizontal deviation has become well established.

2. In general, a vertical deviation of more than 15 Δ is best corrected as a primary operation, or at least together with whatever surgical correction the horizontal component requires.

3. If the vertical deviation is greater in amount than the horizontal deviation, it should be operated on first. It should be remembered that a 15-Δ vertical deviation is much more significant than a 15-Δ horizontal deviation.

4. When the horizontal imbalance is marked, it may not be possible to study the vertical imbalance properly. In such cases the horizontal deviation should be corrected first, the correction of the vertical deviation being left until it can be accurately studied.

5. If the vertical heterophoria or heterotropia associated with the horizontal deviation is slight, surgical correction of the horizontal deviation should be carried out first. This may be followed later, if needed, by operation to correct the vertical deviation.

6. When convergent strabismus is associated with a moderate overaction of the inferior oblique muscles, it is possible that correction of the horizontal defect may throw the ocular alignment away from the chief field of action of the inferior oblique muscles and minimize their effect. Thus, in many instances the inferior obliques need not be touched after the horizontal defect has been corrected.

7. In cases of convergent strabismus in which it is thought best not to correct the vertical deviation first, there is less danger of an overcorrection if the first procedure is resection of one or of both lateral rectus muscles, recession of the medial rectus muscles being left for a finer adjustment, if desired.

8. In the higher degrees of horizontal deviation associated with higher degrees of vertical deviation, operation should be performed for the two components at the same time. If the horizontal deviation is of considerable size, there is little hope of a cure by the removal of the vertical deviation alone. In unilateral strabismus surgical correction of the horizontal and vertical deviations can be satisfactorily carried out at the same time. The most frequent combination is unilateral convergent strabismus associated with an overacting inferior oblique of the same eye.

9. The usual surgical procedures for horizontal defects will produce an overcorrection or an undercorrection if a vertical deviation is present. For example, in uncomplicated convergence excess, recession will give a satisfactory result. However, when a vertical imbalance is present, an equal amount of recession for an equal amount of horizontal squint will result occasionally in undercorrection, but more frequently in overcorrection. This result may either develop immediately after operation or be delayed.

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EXPERIMENTAL STUDIES ON EARLY LENS CHANGES AFTER ROENTGEN IRRADIATION

III. Effect of X-Radiation on Mitotic Activity and Nuclear Fragmentation of Lens Epithelium in Normal and Cysteine-Treated Rabbits

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IN RECENT investigations, Buschke, Friedenwald, and associates,[1] and Smelser and Pfeiffer [2] studied cell division and the influence of ionizing radiations on this function in the corneal epithelium of rats. Mitosis in the lens epithelium has not previously been subjected to comparable investigation, and a few reported figures have given the impression of an extremely low rate of division in this cell layer as a whole.[3] The improved technique for preparing total flat mounts of the lens epithelium attached to the anterior portion of the lens capsule, which was worked out recently by Dr. Alma Howard,[4] provides a means of obtaining reliable estimations of the mitotic index and suggests the possibility of approaching in this way the problem of the effect of radiation on cell division and of testing partial chemical protection against x-ray damage of the mammalian lens.

To these ends the present tripartite study was undertaken: first, to determine the mitotic activity in the anatomically distinguishable zones of the lens epithelium in normal rabbits; second, to observe the changes in the mitotic indices of these zones at various time intervals after the exposure of the eye to a single dose of x-rays, and, third, to compare the phases of inhibition, recovery, and overcompensation of cell division in irradiated untreated animals with the same phases in animals in which relative protection against x-ray damage to the lens had been

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This study was also supported by the Knapp Memorial Foundation.

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achieved by intravenous injection of the amino acid cysteine. Parallel observations on the extrusion of Feulgen-positive material as a sign of early nuclear damage were made and interpreted in the same preparations used for the counts of cells in mitosis.

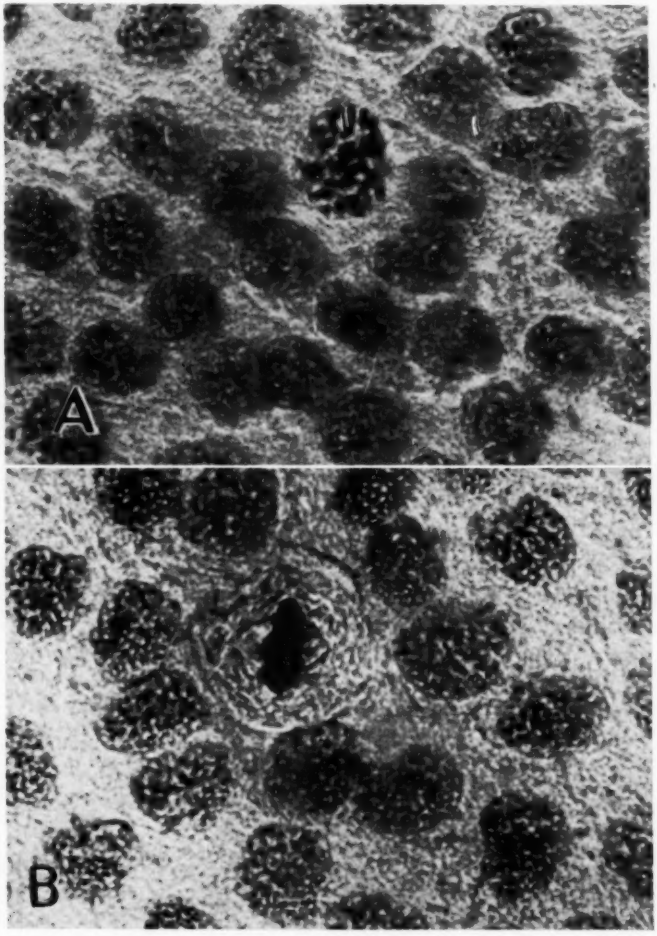

Fig. 1.—Mitotic figures in the lens epithelium of normal rabbit eyes. Feulgen reaction; × 1,560. *A*, prophase; *B*, metaphase.

MATERIAL AND METHODS

In general, chinchilla rabbits, 12 to 16 weeks old, were used for the analysis of cell division in the lens, and about 200 preparations of the epithelium were examined. Additional studies were made to relate age to the incidence of mitosis (26 preparations). The techniques developed by Dr. Howard [4] for preparing the lens epithelium in flat mounts and for carrying out the

Feulgen reaction were followed closely. Minor modifications consisted in removing deposits from the pigmented ciliary epithelium on the lens surface by brushing it cautiously with wet filter paper and in neutralizing the gelatin which served as mounting material in order to prevent early bleaching of the preparations.

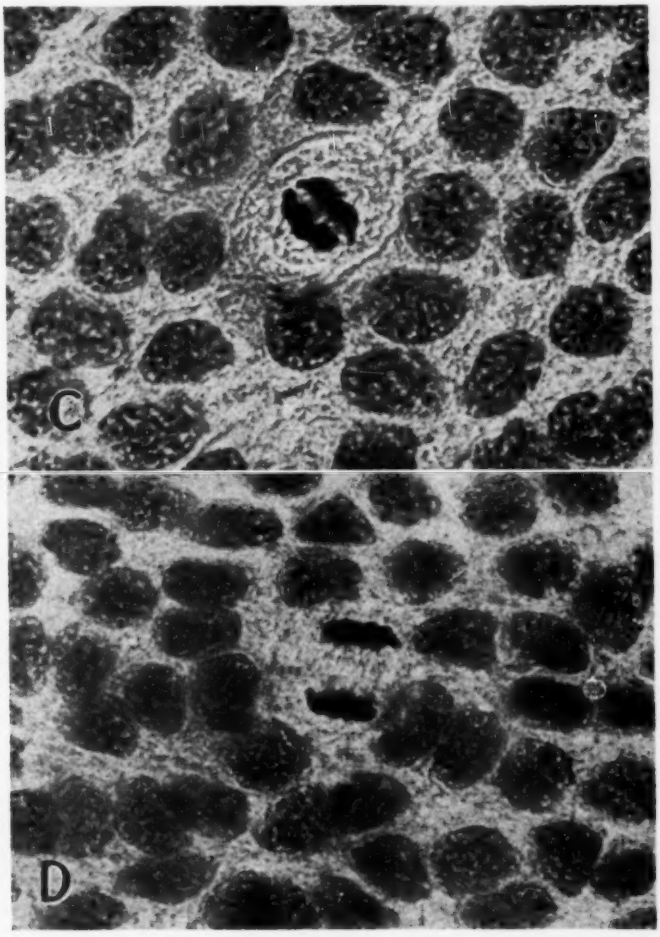

Fig. 1 (cont.).—*C*, anaphase; *D*, telophase. Feulgen reaction; × 1,560.

In order to estimate the number of cells in total epithelium preparations, the slides were projected on a paper screen under a measured magnification, and drawings were then made of the total preparations divided into central, preequatorial, equatorial, and postequatorial zones. In each drawing these zonal areas were measured planimetrically in square centimeters. The cells in each zone were counted under a magnification of 420 by use of Ehrlich stops in many microscopic fields; average values were obtained for each zone. With the formula $A/a \times$ counts (A being the projected area, in square millimeters, and a, the area outlined by the

Ehrlich stop and corrected by the magnification factor to A), the number of cells in the entire preparation and in each zone was estimated.

The number of cells in mitosis was determined by examining the whole preparation under a magnification of 420. This laborious procedure could not be simplified by the use of meridional strips or representative small sectors of known dimensions, as has been done in similar examinations on the corneas of rats [1] and the skin of mice,[5] since the distribution of dividing cells in any of the portions of the epithelium was not uniform enough to avoid major errors through such a time-saving step. In the differential counts of mitotic phases, early prophases and late telophases were not included. Mitotic figures which were the basis for these counts are illustrated in Figure 1.

In the present study only one dose of penetrating x-rays, i. e., 1,500 r, was administered. The radiation factors and the technique of the irradiation were the same as those employed in previously reported work.[6] The dose was selected to permit direct comparison with the results of the earlier studies. Light anesthesia with pentobarbital sodium preceded the irradiation of one eye of the rabbit. The other eye was protected and outside the beam during the procedure. The animals were quickly killed with a large dose of pentobarbital sodium at intervals varying, in the main series, from 30 minutes to 20 days after termination of the x-ray treatment; both eyes were then handled identically, according to the technique of Howard. A smaller number of examinations (nine preparations) were made of the lens epithelium from eyes in which irradiation had preceded enucleation by more than three weeks. These lenses showed opacities in various stages of development.

The influence of cysteine treatment on the effect of x-rays on mitosis was investigated by the intravenous use of 2 gm. of cysteine base dissolved in 16 cc. of distilled water. The amino acid was injected immediately after irradiation of the right eye and 30 minutes prior to irradiation of the left eye. In this series of 55 preparations the same time intervals were permitted to elapse between irradiation and enucleation of the eyes as in the series in which the animals were irradiated without treatment with cysteine. In this group, examinations one-half hour after the use of x-rays were omitted.

RESULTS

Mitosis in Lens Epithelium of Normal Rabbits.—In separating the epithelium with the anterior capsule from the bulk of the lens, traces of epithelium often remained attached to the surface of the anterior cortex, but the resultant small defects of the cell layer in the mount were seen exclusively within the large central portion, where mitosis rarely occurred. Remnants of pigment from the ciliary processes and remnants of lens fibers sometimes obscured in spots the pattern of the epithelium. These more serious obstacles to accurate counting could be greatly reduced by careful removal of these disturbing tissue elements immediately before or after separating the capsule and epithelium from the cortex. Preparations could not be used when spontaneous rupture of the lens capsule occurred during dehydration or hydrolyzation. In the average preparation it was possible to differentiate without difficulty the nuclei of the lens bow from the nuclei of the meridional rows and the postequatorial zone. The germinative zone *sensu strictiori,* with its densely packed nuclei and high content of desoxyribosenucleic acid, and the preequatorial

5. (*a*) Knowlton, N. P.; Hemplemann, L. H., and Hoffmann, J. C.: Effect of X-Rays on Mitotic Activity of Mouse Epidermis, Science **107**:625, 1948. (*b*) Knowlton, N. P., Jr., and Widner, W. R.: Use of X-Rays to Determine the Mitotic and Intermitotic Time of Various Tissues, Cancer Res. **10**:59, 1950.

6. (*a*) von Sallmann, L.; Dische, Z.; Ehrlich, G., and Munoz, C. M.: Study on Penetration of Cysteine and Cystine into the Aqueous Humor of Rabbits and Its Relation to Early X-Irradiation Effects on the Eye, Am. J. Ophth. **34**:95 (May, Pt. 2) 1951. (*b*) von Sallmann, L.: Further Efforts to Influence X-Ray Cataract by Chemical Agents, A. M. A. Arch. Ophth., to be published.

zone, with its more loosely arranged cells, could be distinguished from each other comparatively well, but the transition from the cells of the preequatorial zone to the large cells of the central area, with their poorly staining nuclei, is gradual, and the distinction between these two areas was somewhat arbitrary.

Measurements of the areas and cell counts of preparations obtained from three normal animals gave an average figure of 790,000 cells per lens epithelium, and in 66 eyes of the young adult group the number of cells in division varied per preparation from 100 to 280.[7] As may be seen in Table 1, the counts in the two eyes of individual animals did not differ from each other by more than 10%. The over-all mitotic index of the lens epithelium, i. e., the ratio of the number of dividing cells to the number of resting elements, ranged from 18:100,000 to 27:100,000. This ratio varied greatly from zone to zone. Mitosis could not be demonstrated in the nuclei of the lens bow in any of the normal or irradiated animals. Dividing

TABLE 1.—*Mitotic Counts in Lens Epithelium of Normal Rabbits in Different Age Groups*

Rabbit No.	Age	Total No. of Mitotic Figures in Lens Epithelium		% Difference Between Right and Left Eyes
		O. D.	O. S.	
382	12 days	440	Lost	....
390	12 days	531	500	5.82
378	4½ wk.	345	340	1.45
379	4½ wk.	376	365	2.92
L. M. I A	12-16 wk.	154*	182	....
L. M. I B	12-16 wk.	264	Lost	....
L. M. II A	12-16 wk.	216	134*	....
L. M. II B	12-16 wk.	118*	229	....
L. M. III A	12-16 wk.	111	104	6.3
L. M. III B	12-16 wk.	216	Lost	....
L. M. IV A	12-16 wk.	121	132	8.34
L. M. IV B	12-16 wk.	143	154	7.15
T. 76	16 mo.	26*	80	....
61	20 mo.	22	22	0.00
65	20 mo.	Lost	95	....

* Counts were inaccurate because of defective preparations (preparations incomplete or covered excessively with pigment).

cells were seen only rarely in the meridional rows, were seen in small numbers in the zone between the rows and the germinative area (6:100,000), and were sparse in the central portion of the epithelium (0.11:100,000). The ratios of dividing to resting cells were highest in the densely arranged elements of the germinative area (60:100,000) and in the area to which the name "preequatorial zone" was applied (28:100,000).

Attempts were made to determine diurnal changes in the mitotic activity so far as they could be demonstrated by counting the dividing cells in the morning and again in the evening. In four rabbits, one eye was removed with the animal under ether anesthesia at 9:00 a. m.; the other, at 9:00 p. m. Since late effects of the ether anesthesia on cell division in the second eye could not be excluded,

7. In a personal communication, Dr. Howard stated that she found something like 400 dividing cells per epithelium in the normal lens from 12-week-old rabbits. The lower average in the series reported here could be explained by the omission of very early and late stages of cell division.

comparative examinations were carried out on eight litter mates by killing some animals of a litter in the morning and others in the evening of the same day. Table 2 shows that in the majority of experiments more dividing cells were found in the evening hours. This was in contrast to the diurnal variations described by Knowlton, Hemplemann, and Hoffmann [5a] with reference to the skin of mice. The variability in the counts of dividing cells of normal animals indicated that factors other than diurnal influences were responsible for shifts in individual counts; the impression was gained, for example, that the warm, humid summer days in New York exerted a depressing effect on the cellular function studied.

The examination of three normal animals about 2 years of age yielded counts between 22 and 87, that is, far below the average for the group of young mature animals. Counts in both eyes of two rabbits 12 days of age, on the other hand, exceeded about twice the average for the young adult group (Table 1). In all age groups the germinative zone contained the greatest number of dividing cells, and the central area, the lowest number, with the nuclei of the lens bow apparently always in the resting phase.

TABLE 2.—*Diurnal Changes in Mitotic Activity in Normal Lens Epithelium* *

Rabbit No.	No. of Mitotic Figures		Litter Mates	No. of Mitoses			
				A. M.		P. M.	
	A. M.	P. M.		O. D.	O. S.	O. D.	O. S.
374	(O. D.) 169	(O. S.) 137	L. M. I A	154	182	...	...
375	(O. D.) 105	(O. S.) 135	L. M. I B	...	...	204	†
376	(O. S.) 123	(O. D.) 166	L. M. II A	216	†	...	...
377	(O. S.) 119	(O. D.) 194	L. M. II B	...	...	229	†
			L. M. III A	111	94	...	...
			L. M. III B	...	...	216	Lost
			L. M. IV A	121	182	...	...
			L. M. IV B	...	...	143	154

* Comparisons are made of right and left eyes of individual animals and of litter mates.
† Defective preparations.

Effect of Local Irradiation of Eye with 1,500 r on Mitotic Activity of Lens Epithelium.—According to the irradiation technique employed in these experiments, the nonirradiated, shielded eye may have been subjected to stray radiation of about 5 r.[8] If it is assumed that this amount of x-radiation did actually strike the protected lens, it may be concluded that the small dose did not affect the rate of mitotic activity in a series of 33 animals; the total and differential counts per zone did not deviate significantly from comparable counts in normal (nonirradiated) animals.

The lens epithelium of eyes removed 30 minutes after direct x-irradiation with 1,500 r showed in two animals five and eight mitotic figures, respectively, and a high incidence of cells in late telophase was noted at this time; as usual, they were not included in the counts. At the one-hour interval the preparations were completely free of dividing cells, whereas the contralateral (control) eyes gave counts in the normal range. The light anesthesia with a barbiturate employed during the

8. von Sallmann, L.: Experimental Studies on Early Lens Changes After Roentgen Irradiation: I. Cytological and Morphological Changes, A. M. A. Arch. Ophth. **45**:149 (Feb.) 1951.

irradiation procedure, therefore, did not have a noticeably depressive effect. The complete, or almost complete, inhibition of cell division in the lens epithelium of eyes which had been exposed to 1,500 r lasted three or four days. The phase of recovery then set in, and an average normal level of mitotic activity was reached on about the ninth day. The succeeding period was characterized by a compensatory increase in the proportion of dividing cells to about twice the normal average count. In seven instances overcompensation was observed for one week but seemed extended in four animals for at least another week (Fig. 2). The observations in the main series were not prolonged beyond three weeks, in view of the progressive reduction in the number of cellular elements, especially in the germinative zone, which made it impossible to establish comparable ratios between dividing and resting cells and thus to follow the changes in the mitotic rate in these later

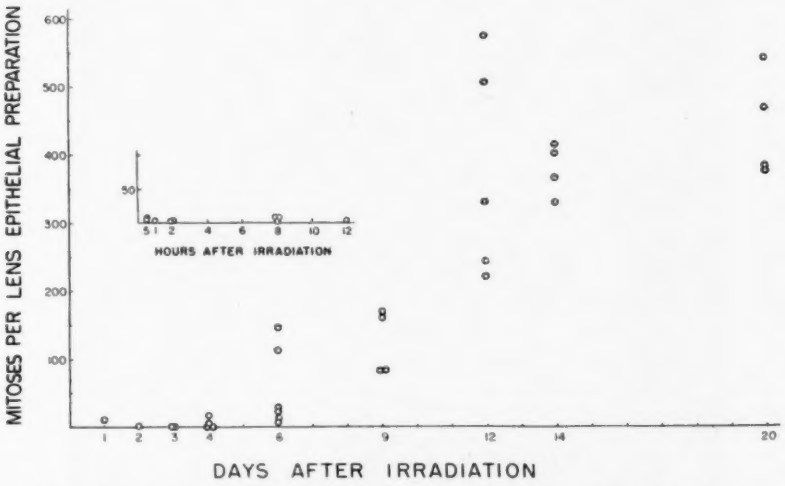

Fig. 2.—Effect of x-irradiation (1,500 r) on mitotic activity in rabbit lens epithelium.

stages on a reliable basis. The overshooting of cells in mitosis was observed in all areas of the epithelium but was most striking in the germinative zone.

Structural alterations in the mitotic figures occurred frequently during the period of recovery and of compensatory increased cell division. There were defects in the orientation of the figures, clumping of chromosomes in metaphase and anaphase, formation of chromosome bridges in anaphase and telophase, and chromosome fragmentation with separation of chromatin particles. Clumping of chromatin material in late prophase and metaphase was sometimes associated with the extrusion of Feulgen-positive material into the cytoplasm and with the early stages of nuclear fragmentation (Fig. 3). Pyknosis was observed as a result of chromatic clumping.

The phenomenon of dispersion of clumped chromatin globules in the cytoplasm was first observed in elements with rounded cell bodies without disruption of the

nuclear membrane and was encountered occasionally in one to two cells of normal epithelium in preparations from nonirradiated rabbits. This might be the expression of the physiological death of growing cells. In the irradiated eyes, more nuclei

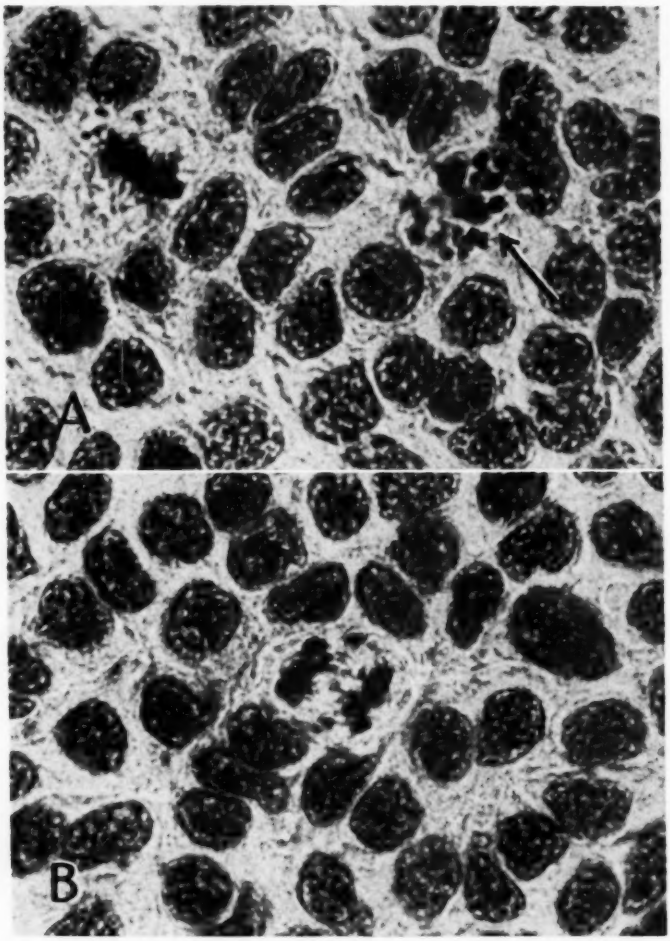

Fig. 3.—Pathologic reactions in lens epithelium of rabbit eyes receiving 1,500 r of x-radiation. Feulgen reaction; × 1,560. *A*, prophase with clumped chromosomes; *B*, anaphase with translocation of chromosomal material and tendency to produce bridges.

appeared to be affected soon after irradiation, and the various stages of nuclear fragmentation could be followed well with the Feulgen reaction. Under the conditions of the experiment, abnormal extrusion of chromatin material from the nuclei began two hours after irradiation, increased greatly at the end of the inhibitory

phase, and was particularly pronounced in the following period of the exaggerated mitosis (Table 3). In some instances pathological mitoses apparently led to nuclear fragmentation. Later, the preparation showed scattered, round, irregularly

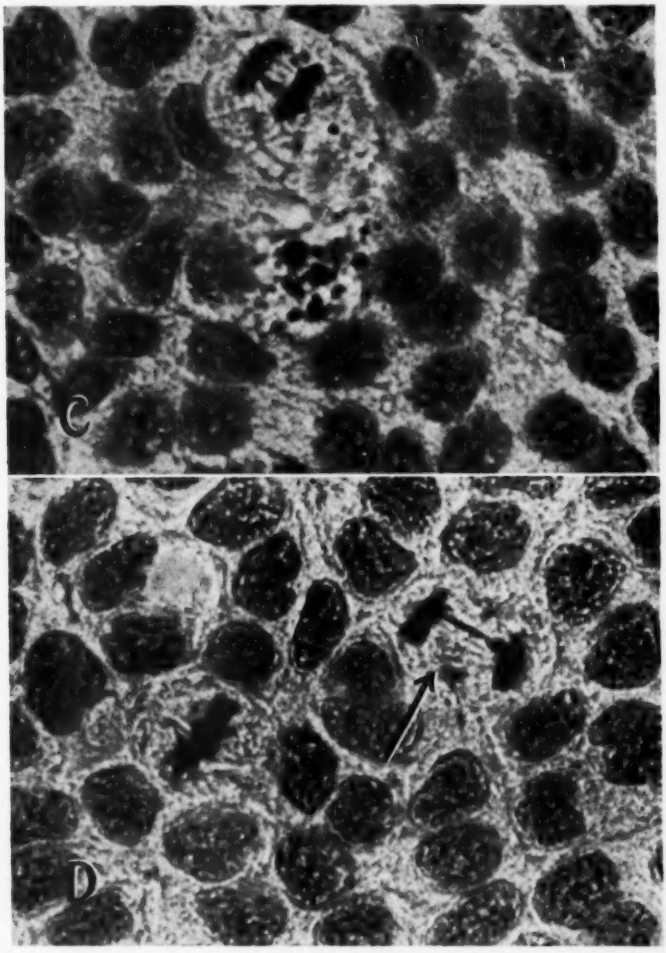

Fig. 3 (cont.).—*C*, anaphase with chromosome bridge and accumulation of Feulgen-positive material as residue of nuclear fragmentation; *D*, telophase with chromosome bridge (chromosomal material attached to spindle fibers). Feulgen reaction; × 1,560.

sized particles of Feulgen-positive material, as remnants of the liquefied and vacuolated cell bodies interrupted the normal mosaic of the epithelial pattern. Cogan and Donaldson [3b] observed fragmentation of nuclei in clear lenses of irradiated rabbits three weeks after the use of 1,500 r with a voltage of 1,200 kv.

In general, the frequency of nuclear fragmentation was greatest in the germinative zone; the rate was high also in the preequatorial and postequatorial areas and relatively low in the large central portion. The decrease in the actual number of cells in the periphery of the lens epithelium in the late stages of x-ray damage could be shown as convincingly in the flat preparations as in the meridional sections examined in the course of previous studies [8] (Fig. 4). This observation illustrated the common radiobiological experience that nuclear destruction is encountered predominantly in regions of active cellular proliferation and may be considered a precursor of subsequent depletion of cellular elements. The comparatively high content of desoxyribose nucleic acid in the nuclei of this part of the

TABLE 3.—*Extrusion of Feulgen-Positive Material in Lens Epithelium of Eyes Given a Single Dose (1,500 r) of X-Radiation and of Normal (Control) Eyes*

Rabbit No.	T*	No. of Cells with Nuclear Fragmentation: Irradiated Eyes	No. of Cells with Nuclear Fragmentation: Control Eyes	Rabbit No.	T*	No. of Cells with Nuclear Fragmentation: Irradiated Eyes	No. of Cells with Nuclear Fragmentation: Control Eyes
383	½ hr.	0	0	286	.....	117	1
384	.....	0	0	370	.....	38	Lost
356	1 hr.	0	0	365	9 days	20	0
307	2 hr.	0	0	304	.....	70	0
354	.....	5	1	339	.....	93	Lost
298	8 hr.	0	0	338	.....	91	0
396	O. D.	2	..	284	12 days	440	2
396	O. S.	3	..	332	.....	124	0
300	12 hr.	6	0	339	.....	140	Lost
296	24 hr.	5	0	400	O. D.	152	..
292	2 days	6	1	400	O. S.	98	..
373	3 days	5	Lost	285	.....	386	..
283	.....	117	0	331	14 days	102	0
311	4 days	8	1	288	.....	219	0
401	.....	42	..	287	.....	179	0
402	O. D.	21	..	328	20 days	138	0
402	O. S.	27	..	318	.....	230	0
393	.....	54	1	317	.....	97	0
309	6 days	4	1				
394	.....	48	0				
395	.....	124	0				

* T indicates time after irradiation.

epithelium suggests that the degree of radiosensitivity could be related to the cytochemical characteristics of these cells.

Influence of Cysteine Treatment on X-Ray Effect on Mitosis in Lens Epithelium.—It was shown in a previous study [6b] that all early microscopically visible signs of radiation damage to the lens were influenced by pretreating experimental animals with a large dose of cysteine shortly before their exposure to x-rays. It was possible to demonstrate a clear difference in favor of pretreatment, in the extent and progression of radiation injury to the lens between the eyes that received the cysteine before irradiation and those that received it after irradiation.

The effect of cysteine pretreatment on x-ray-induced changes in mitosis was complex in character and will need further study. It will be recalled that the amino acid was injected immediately after irradiation of the right eye and 30 minutes prior to the irradiation of the left eye. Complete inhibition of mitosis set in in both

eyes of these cysteine-treated animals shortly after their exposure to 1,500 r. Although in the following hours and days a few cells appeared to have escaped the inhibitory influence of the irradiation, a general suppression of mitotic activity persisted for nine days in both eyes. In the subsequent periods of recovery and

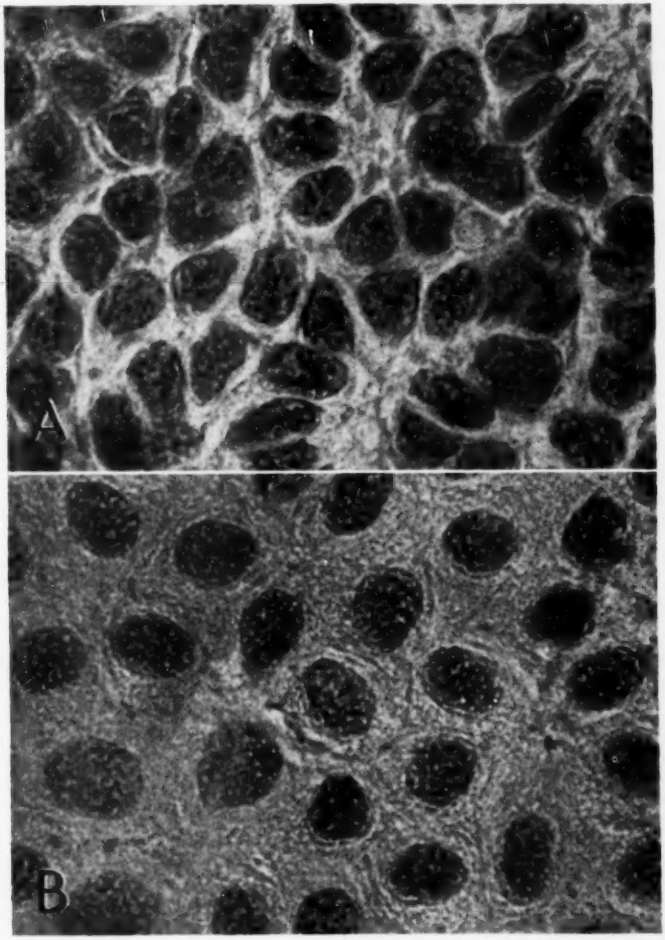

Fig. 4.—Germinative zone (*A*) in normal lens and (*B*) in lens receiving 1,500 r of x-radiation several months prior to enucleation. Feulgen reaction; × 1,560.

overcompensation the individual counts varied greatly. Especially, the values recorded on the 12th day after irradiation were scattered over such a wide range that no conclusions can be drawn with respect to differences between the groups of eyes at this time. The graph (Fig. 5) suggests that the peak of overcompensation

in the nonprotected eyes was not reached before 20 days after irradiation. The eyes irradiated after the use of cysteine showed average readings of similar magnitude two and three weeks after irradiation.

The extent of nuclear fragmentation in cysteine-treated and in untreated animals is compared in Table 4. The number of the cells showing extrusion of chromatin or advanced fragmentation of the nuclei was so great in the late stages that the counts were not highly accurate, but the differences were sufficient to indicate that pretreatment with cysteine was moderately protective against the described nuclear changes.

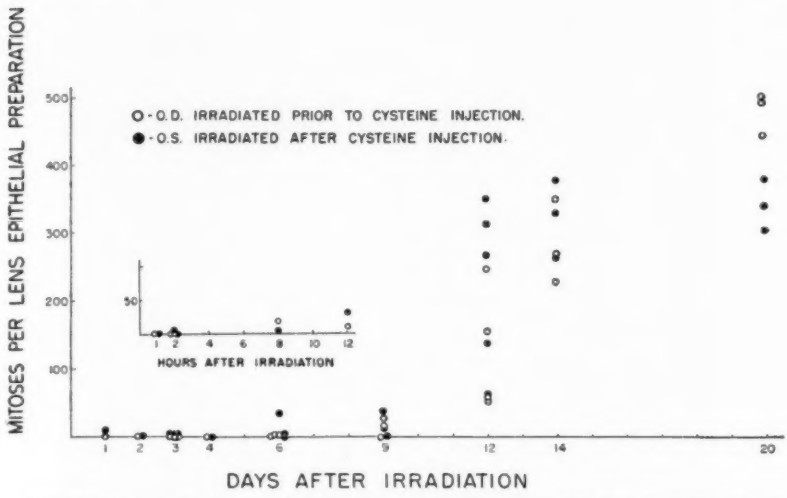

Fig. 5.—Effect on mitotic activity in rabbit lens epithelium of 1,500 r of x-radiation given immediately prior to and one-half hour after intravenous injection of 2 gm. of cysteine base.

TABLE 4.—*Extrusion of Feulgen-Positive Material in Lens Epithelium of Rabbit Eyes Irradiated with a Single Dose of 1,500 r Immediately Prior to (Right Eye) and One-Half Hour After (Left Eye) Intravenous Injection of 2 Gm. of Cysteine Base*

No.	T*	O. D.	O. S.	No.	T*	O. D.	O. S.
346	1 hr.	0	0	316	9 days	28	12
289	2 hr.	0	1	336	.....	27	11
300	.....	0	1	335	.....	20	8
301	8 hr.	0	0	282	12 days	0	0
290	12 hr.	0	0	315	.....	8	17
295	24 hr.	1	0	367	.....	Lost	25
290	2 days	1	0	388	.....	11	5
293	3 days	90	1	389	.....	22	12
471	.....	38	1	270	14 days	0	0
372	.....	3	0	337	.....	78	65
368	4 days	0	1	397	.....	139	67
281	6 days	1	0	271	20 days	161	91
368	.....	2	5	319	.....	612	237
363	.....	8	1	327	.....	61	39

* T indicates time after irradiation.

In five control experiments, observations on the effect of the intravenous injection of 2 gm. of cysteine on mitosis in the lens epithelium were made at intervals of two and eight hours after administration. The results (Table 5) indicated that the chemical exerted no depressive action at this time.

COMMENT

The single-layered lens epithelium, with its relatively large cells, is extremely well suited to the examination of mitotic activity and of fine, x-ray-induced structural lesions. Although techniques for studying this epithelium in total flat mounts were elaborated by earlier investigators (Verhoeff and associates,[9] Poppe,[3a] Cogan [3b]), they were not applied, or could not be applied, to systematic investigations on mitosis. There is still a general impression that only a few mitotic figures can be discovered in the entire epithelium of the lens (Poppe,[3a] Cogan,[3b]), although Rabl,[11] in his fundamental studies (1907), had not infrequently found dividing cells in the germinative zone of the lens epithelium of the rabbit. The new

TABLE 5.—*Mitotic Activity in Lens-Epithelium Preparations from Rabbits Treated with Cysteine Base*

	Total No. of Mitotic Figures in Lens Epithelium			
	2 Hr. After Intravenous Injection of Cysteine Base (2 Gm.)		8 Hr. After Intravenous Injection of Cysteine Base (2 Gm.)	
Rabbit No.	O. D.	O. S.	O. D.	O. S.
361	202	210	...	...
362	118	105	...	...
390	299	310	...	...
308	...	...	157	156
385	...	...	156	168

technique of Howard,[4] which permits the Feulgen reaction to be carried out on the anatomically undisturbed lens, gave satisfactory or excellent results in our hands. The main obstacle—spontaneous rupture of the lens capsule during dehydration or hydrolyzation—did not occur often enough to reflect unfavorably on the usefulness of the procedure.

The need for a great number of examinations when random variations in mitosis are to be considered could not be met as easily in these experiments on rabbits as it could have been if rats or mice had been used. On the other hand, the irradiation of the individual eyes of the experimental animals and the histologic procedures could be carried out with much less difficulty than on the smaller animals, and the results obtained could be well aligned with the results of previous studies on x-ray damage to the lens. These advantages offset in part the disadvantages inherent in the relatively short series of experiments and in the necessity for a laborious counting of large preparations.

The anatomical and cytochemical differences in various areas of the lens epithelium were paralleled by differences in the degree of mitotic proliferation.

9. Verhoeff, F. H.; Bell, L., and Walker, C. B.: Pathological Effects of Radiant Energy on the Eye, Proc. Am. Acad. Arts & Sciences **51**:627, 1916.

10. Footnote deleted.

11. Rabl, C.: Über den Bau und die Entwicklung der Linse: III, Ztschr. wissensch. Zool. **17**:1, 1907.

Thus, the mitotic index of the germinative zone, with its dense arrangement of nuclei rich in desoxyribose nucleic acid exceeded by a multiple the indices for the central and postequatorial areas and was twice the index for the anteriorly adjacent zone. Differences between the counts on eyes removed in the morning and the counts on eyes removed at night could be considered as expressions of diurnal change. In addition to the influence of excitement, sleeping and waking habits, and the food intake of the animal—factors enumerated recently by Bullough [12]—factors such as seasonal influences may have induced some of the variations in our series.

Buschke, Friedenwald and their associates [1] have drawn attention to the fact that the "number of mitoses per area of tissue does not necessarily represent a reliable index of the mitotic activity, since a high number of mitoses may be found either if the rate of entrance into mitosis is increased or if the rate of escape from mitosis is decreased." These investigators obtained confirmatory evidence for their counts by the use of the alkaloid colchicine, which was introduced by Dustin [13] in connection with similar studies on mitotic activity. In the present investigation on rabbits, colchicine arrest of mitosis in metaphase was not used as a tool because of possible side-effects of unknown nature which the alkaloid might have on this experimental animal. There may be some question, therefore, as to whether the number of mitotic figures in the zones of the lens preparations in this study represent mitotic activity in the strict sense.

In the series of experiments in which x-irradiations were employed, standard conditions were observed throughout. The only variable was the time interval between the irradiation and the removal of the eyes. In addition to the effect of 1,500 r on one eye of the rabbit, the effect of low-dosage exposure might have been evaluated from a study of the fellow eyes not directly irradiated, but the dose of 5 r of stray radiation, which was measured occasionally with a Victoreen chamber in the orbit of the nonirradiated side, may not have reached the lens in all instances. It was thus impossible to compare the radiosensitivity of the lens epithelium with that of other tissues which have been exposed to such small quantities of x-radiation.

It is commonly believed that mitosis is one of the earliest functions to be affected by x-irradiation. This was certainly borne out by the almost complete suppression of mitosis in the lens epithelium as soon as 30 minutes after the exposure of the eye to 1,500 r. Since those cells which have entered mitosis at the time of irradiation presumably complete the cycle, the cessation of mitosis 30 minutes after irradiation —signified by the complete, or almost complete, absence of dividing figures at this time—indicated that the time required for mitosis was about 30 minutes. It is believed that in general the intermitotic time is inversely proportional to the mitotic index of a tissue, but special investigations would be needed to establish such a time relation in the various zones of the lens epithelium. A comparison of the influence of x-irradiation on the mitotic activity of the lens epithelium and its influence on the mitotic activity of other tissues does not seem to be warranted until we have at hand the results of experiments in which the technique and dose of the irradiation have been varied.

12. Bullough, W. S.: Mitotic Activity of Carcinogenesis, Brit. J. Cancer **4**:329, 1950.

13. Dustin, P., Jr.: Some New Aspects of Mitotic Poisoning, Nature, London **159**:794, 1947.

Proportionality between the radiosensitivity of cellular elements and their activity in terms of mitotic proliferation was indicated by the excessive nuclear fragmentation in the germinative zone, for which the highest mitotic index had been established. It is commonly assumed that such a relation exists in all tissues, but Jacobson and his co-workers [14] failed to find it in recent studies on erythrocyte precursors in the hemopoietic tissue of rabbits.

The incidence of nuclear fragmentation increased steeply during the phases of recovery and overshooting of mitosis which followed exposure to the x-ray beam, but there was no indication of a causative relation between the two phenomena. The onset of mitotic inhibition clearly preceded by several days the appearance of a high rate of nuclear fragmentation.

Contradictory statements have been made in the literature as to the sensitivity of individual phases of cell division to the suppressing action of x-rays. The evaluation of the differential counts in the specific zones of the lens epithelium at early intervals after irradiation, and the disappearance of mitotic figures 30 minutes after irradiation, with the presence of a considerable number of cells in late telophase, suggest that the terminal stage of interphase and early prophase are most readily inhibited by this ionizing radiation, an observation which would lend support to the opinion of Strangeways and Hopwood,[15] Carlson,[16] Sax and co-workers,[17] Creighton,[18] Marshak,[19] and others.

The action of x-rays on the mitotic activity of the lens epithelium has been shown to be influenced moderately by cysteine treatment. The relation of this influence to the cataractogenic effect of x-rays is not as simple as the difference in the degree of other microscopic signs of x-ray-induced damage between eyes treated with cysteine before irradiation and eyes treated with cysteine after irradiation. In all the cysteine-treated eyes the initial suppression of mitosis was not as complete as it was in the untreated eyes, but the period of inhibition of cell division was prolonged. The delay in recovery of mitosis in the cysteine-pretreated eyes was followed by a period of overshooting of mitotic activity, but the rate of compensatory increase of cell division did not reach the high levels attained in the irradiated eyes of untreated animals or in the eyes which had been irradiated before

14. Jacobson, L. O.; Marks, E. K.; Gaston, E. O.; Simmons, E. L., and Block, M. H.: Studies on Radiosensitivity of Cells, Science **107**:248, 1948.

15. Strangeways, T. S. P., and Hopwood, F. L.: Effect of X-Rays upon Mitotic Cell Division in Tissue Cultures in Vitro, Proc. Roy. Soc., s.B **100**:283, 1926.

16. Carlson, J. G.: Immediate Effects of 250 r of X-Rays on Different Stages in Mitoses in Neuroblasts of Grasshopper Chortophaga Viridifasciata, J. Morphol. **66**:11, 1940; Immediate Effects of 31 r of X-Rays on the Different Stages in the Mitoses of Neuroblasts of Chortophaga, ibid. **71**:449, 1942; Effect of Radiation on Mitosis, in Symposium on Radiation Genetics, sponsored by the Biology Division of Oak Ridge National Laboratory, Oak Ridge, Tenn., March, 1948; Atomic Energy Commission Declassified Document No. ORNL-570, 1950.

17. Sax, L.: An Analysis of X-Ray Induced Chromosome Aberration in Tradescantia, Genetics **25**:41, 1940. Sax, L., and Swanson, C. P.: Differential Sensitivity of Cells to X-Rays, Am. J. Bot. **28**:52, 1941.

18. Creighton, M.: Effect of X-Rays on Mitotic and Meiotic Chromosomes and Cell Division in Chorthippus Longicornis (Orthoptera), J. Exper. Zool. **87**:347, 1941.

19. Marshak, A.: Effect of X-Rays on Chromosomes in Mitosis, Proc. Nat. Acad. Sc. **23**:360, 1947; Effect of X-Rays and Neutrons on Mouse Lymphoma Chromosomes in Different Stages of the Nuclear Cycle, Radiology **39**:621, 1942.

the use of cysteine. It can thus be concluded that the interference of cysteine with activated chemical reactions which are caused by the ionizing radiation modified quantitatively to a small extent the effect on mitosis of a dose of 1,500 r of penetrating x-rays. It is planned to vary the technique of irradiation in order to obtain more information on the nature of biochemical influences on effects of x-rays in the lens.

SUMMARY AND CONCLUSIONS

On the basis of cell counts of preparations of the entire lens epithelium of normal mature rabbits, the number of cell elements was estimated to be approximately 790,000. The range of the mitotic index for the total preparation was found to be from 18 : 100,000 to 27 : 100,000. The distribution of dividing cells varied characteristically in the various anatomic zones of the epithelium: The highest index (60 : 100,000), in the germinative zone, contrasted with the index of 0.11 : 100,000, in the spacious central area, and with the apparent absence of mitosis in the nuclei of the lens bow.

Exposure of the rabbit's eye to the beam of x-rays (1,500 r) was followed by almost complete disappearance of dividing cells 30 minutes after irradiation. This total inhibition lasted three to four days. Recovery of mitosis took place in the next four days and was followed by a period of overcompensating increase in the proportion of dividing cells, which could be observed for at least one more week.

Nuclear fragmentation and extrusion of Feulgen-positive material in the form of clumped chromatin globules began 2 hours after irradiation. There was a steep rise in the incidence of this sign of radiation injury when the inhibition of mitosis terminated, particularly when the overshooting phenomenon had fully developed. A relative depletion of cell elements, which was most striking in the equatorial zones, was considered a result of this nuclear fragmentation, which led characteristically to the liquefaction of cell bodies with vacuole formation.

Cysteine treatment of irradiated animals prolonged the inhibitory effect of x-rays on mitosis, slowed the speed of recovery, and reduced the extent of overshooting of cell division, particularly when the cysteine was injected prior to the exposure of the eye to 1,500 r.

The relative protective action of pretreatment with cysteine against x-ray damage of the lens was demonstrated in this study by a lower incidence of nuclear fragmentation in all zones of cysteine-pretreated eyes as compared with the incidence of this type of damage in the eyes of untreated irradiated rabbits and of rabbits treated after irradiation.

Dr. Roberts Rugh gave constructive criticism in the preparation of this paper, and Dr. B. Pillat took the photomicrographs.

FACIAL DEFORMITY IN ACROCEPHALY AND ITS SURGICAL CORRECTION

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THE CLINICAL picture of acrocephaly [1] or related craniostenoses includes a characteristic pattern of facial deformity, consisting primarily of exophthalmos, aplastic, recessed maxilla, and hypertelorism.[2] Ptosis and strabismus are often present. The underdeveloped maxilla is responsible for the flatness of the anterior facial region and the recessed floor of the orbit. The nose is frequently described as wide and curved or as, in the French literature, *becque de perroquet*. The palate is usually contracted and high-vaulted. If the alveolar process is recessed with the rest of the maxillary compound, the protrusion of the normally developed mandible (relative prognathism) adds another factor to the facial malformation. The same facial appearance is also characteristic of craniofacial dysostosis (Courzon's disease), which many authors consider identical with acrocephaly.

Acrocephaly has always attracted the attention and interest of ophthalmologists. Next to mental deficiency, optic nerve atrophy, leading to blindness, is the most serious symptom of acrocephaly. It affects about one-third of the patients who are reported with the fully developed deformity.

Because the exophthalmos, and sometimes the hypertelorism, is the most prominent manifestation, the patient is usually referred to an ophthalmologist. Occasionally the differentiation from other forms of exophthalmos may present a problem. The severity of the exophthalmos may be such as to result in lagophthalmos. Cases of anterior dislocation of the eyeball from the orbit have been reported.[3]

The clinical picture, pathology, and etiology of acrocephaly were thoroughly discussed by Ferriman [4] and described in 264 articles (in English, French, and German) published before 1941, which he cites in his bibliography. Numerous other papers on the subject have appeared in the last decade.

From St. Joseph Hospital, Paterson, N. J.

1. This term is used in preference to oxycephaly, since it is accepted by the *Quarterly Cumulative Index Medicus*. The descriptive terms turricephaly, scaphocephaly, and plagiocephaly are based on the various configurations of the cranium but designate basically the same syndrome.

2. This term is used to define a symptom, exaggerated intraocular distance, rather than to indicate the skeletal anomaly described by D. M. Grieg (Hypertelorism, Edinburgh M. J. **31**:560, 1924).

3. Sherne, J.: Dislocation of the Eyeball as a Complication of Oxycephaly, Brit. M. J. **1**:565, 1938.

4. Ferriman, D.: Acrocephaly and Acrocephalosyndactyly, London, Oxford University Press, 1941.

In brief, the underlying mechanism of the deformity is considered to be a deficiency in growth. This manifests itself in an early fusion of the cranial bones (premature ossification of suture lines), and hypoplasia of the craniofacial skeleton. Different areas may be involved, and to a variable degree, thus accounting for the divergence in the clinical picture. The anomaly of the facial skeleton is further influenced by the secondary changes, the compensatory development of the cranial cavity in other directions. The extension of the middle cranial fossa thrusts the greater wings of the sphenoid bone forward and medially. Since they represent the posterior lateral walls of the orbit, this process results in a shallow orbit. The distortion and widening of the lesser wings of the sphenoid bone may result in an exaggerated spread of the orbit, i. e., hypertelorism.

The clinical picture of acrocephaly runs the gamut of extreme deformity of the craniofacial skeleton, usually depicted in textbooks, to mild anomalies, bordering on

Fig. 1.—*A* and *B*, facial configuration strongly suggestive of a mild acrocephalic deformity, with no corroborating findings. Note exophthalmos, flatness of the maxilla, and slight apparent hypertelorism. This condition was observed incidentally when the patient sought surgical attention because of a traumatic lesion on the forehead.

the normal. Ferriman [4] pointed out that in the investigation of the hereditary pattern of acrocephaly many mild forms are not recognized, since they approach the normal variations of the facial skeleton. In such mild cases the abnormal configuration of the skull is usually absent. Most of the roentgenologic changes are due to increased intracranial pressure. Frequently, such pressure does not rise high enough to produce anatomical or functional symptoms. Normal fusion of the cranial bones is variable in time and occurs late in life (about the age of 30). Failure to demonstrate the obliteration of the suture lines in the case of a child or an adolescent does not contradict the diagnosis of mild acrocephaly. While cases of fully developed acrocephaly are relatively rare, cases of the mild form are undoubtedly common. I am inclined to believe that the facial deformity is often more prominent in childhood and that it improves with maturity (Fig. 1*A* and *B*).

In cases of severe acrocephaly with mental deficiency or approaching blindness, the accompanying facial disfigurement is obviously only of academic interest. However, there are cases of acrocephaly with no essential functional impairment in which the anomalous configuration of the facial skeleton represents a serious cosmetic handicap. The patient finds the deformity a severe obstacle in leading a normal, constructive life and develops the typical psychologic reaction characteristic of any facial disfigurement—social withdrawal and lack of self-confidence.

Surgical efforts to alleviate the facial deformity in acrocephaly have found little expression in the literature. Gillies and Harrison [5] presented a case of acrocephaly in which the recessed maxilla was chiseled free of all its attachments and brought forward. The proper occlusal relation between the maxilla and the mandible was established and maintained by intermaxillary wiring. Although gradual recession occurred during the ensuing months, considerable improvement in the facial contour was achieved.

Cases in which the hypoplastic maxilla resulted in an abnormal relation of the maxilla to the mandible, causing an apparent mandibular prognathism, have been reported by Kostečka.[6] He performed a horizontal osteotomy of the ascending ramus to bring about a more harmonious relation of the lower part of the face and to obtain a satisfactory dental occlusion.

REPORT OF A CASE

My patient, a nurse aged 25, was first seen in 1950. There was no history of any facial anomaly in the family, neither the parents nor the siblings showing any suggestion of the affliction. The patient was the youngest of three children and was born to a 40-year-old mother, who allegedly was not well during the pregnancy. The delivery was prolonged and difficult. The child was born on the verge of asphyxia because of the torsion of the umbilical cord. During the first few days it was noted that the infant had conspicuously protruding eyes and was unable to open them. Her inability to raise her lids persisted during infancy and childhood but gradually improved at the beginning of adolescence. With the growth of the facial skeleton, the protrusion of the eyeballs seemed somewhat less pronounced.

The patient went through normal schooling. Before being accepted for nurses' training, she was thoroughly examined and told that her exophthalmos was due to a congenital anomaly, that it was stationary and had no functional implications.

She had always been acutely aware of her facial disfigurement, particularly of the severe exophthalmos, and was eager for any improvement which surgery could give her.

Examination revealed a well-built and well-proportioned young woman, who was alert and of normal mental capacity. The configuration of the cranial vault was normal. The facial appearance can be seen in Figure 2*A* and *B*. There was a striking protrusion of both eyeballs, emphasized by the recession of the infraorbital and zygomatic regions. The lower lid extended in front of the plane of the cheek. There was mild ptosis of the lids, particularly noticeable when the patient looked upward. The eyes were widely separated.

The projection of the lower part of the maxillary compound was normal, so that both lips and the lower third of the face were in harmonious relation. The nose was large and showed a lateral curvature, with a wide, flat bridge.

The intraoral examination showed a well-developed dentition and satisfactory intermaxillary occlusion. The palate was high-vaulted. Anterior rhinoscopy showed no abnormalities. The last

5. Gillies, H., and Harrison, S. H.: Operative Correction by Osteotomy of Recessed Malar Maxillary Compound in a Case of Oxycephaly, Brit. J. Plast. Surg. **3**:123, 1950.

6. Kostečka, F.: Ein Beitrag zur Dysostosis craniofacialis, Ztschr. Stomatol. **35**:113, 1937.

complete ophthalmologic examination, a few years previously, was reported on as follows: exophthalmos, 30 mm. in the right eye and 29 mm. in the left eye; intercaruncular distance, 43 mm.; interpupillary distance, 72 mm.; a remote convergence near point, and mild nystagmus on lateral motion. Vision was 20/40 in the right eye and 20/30 in the left eye; after correction of far-sighted astigmatism, it became 20/25 in each eye. The fundi were normal. Binocular and stereoscopic vision was good.

Roentgenologic examination of the skull (Fig. 3), by Dr. Frank Schell, revealed extensive digital indentation, exostosis, and thinning of the bone throughout the cranial vault. The posterior sweep of the orbit was shallower than normal. The maxillary sinuses were very small, and the maxillae were recessed beneath the orbits. The orbital foramina were normally placed and of normal size. The frontal sinuses were well developed. The cranial sutures were obliterated.

Comment.—The roentgenologic findings in the cranial vault, the high palatal vault, the aplastic maxilla, and the characteristic facial appearance justified the

Fig. 2.—*A* and *B*, preoperative appearance of the patient described in the text.

diagnosis of acrocephaly in spite of the normal configuration of the skull. Some degree of hypertelorism may have been simulated because of the divergence of the axis of the eyeball; but the deformity was also real, as attested by the increased intercanthal distance.

In analyzing a surgical approach to obtain any degree of improvement, I concluded that the procedure of Gillies was not applicable in this case because of the presence of a satisfactory dental occlusion and harmonious relations between the alveolar portion of the maxilla and the mandible. Therefore, it was decided to correct the recession of the maxilla by reinforcing the infraorbital and zygomatic regions with a bone graft, which would also extend the floor of the orbit.

Operation (March 17, 1950; St. Joseph Hospital).—Anesthesia was induced with thiopental sodium and nitrous oxide, supplemented by ether insufflation. Through a curved incision in the

crease of the lower lid, the orbital margin was exposed, and by blunt dissection the soft tissues were elevated from the infraorbital and lateral zygomatic region. The infraorbital nerve was preserved and gently stretched. The same exposure was carried out on both sides. The left iliac crest was exposed in a routine manner. A large bony fragment was removed from the crest of the ilium with osteotomes. The bone graft was broken into small chips; the cancellous component was utilized chiefly, but was mixed with some of the cortical elements in order to obtain more bulk. The bony chips were inserted into the prepared pockets on the face, and the desired contour was molded by digital manipulation. The facial incisions were closed in two layers. The iliac incision was closed in a routine manner without a drain.

Pressure dressings on the face were maintained for five days, after which the sutures were removed and dressings discontinued. The patient was then discharged from the hospital. There was a great deal of periorbital edema, which took a few weeks to subside. At first it appeared

Fig. 3.—X-ray picture of the patient's skull, showing pronounced digital indentations, increased vascular pattern, shallow orbit, and underdeveloped maxillae with small maxillary sinuses. The alveolar process of the maxilla comes forward into satisfactory occlusion with the mandible.

that the area was overcorrected and somewhat uneven and lumpy. Manual massage and the use of an electric vibrator were recommended. Gradually a smooth, even outline was established. The scar was hardly detectable. The patient returned to work after about one month.

Operative Result.—The middle-face contour was greatly improved, and the disproportionate relation between the eyeballs and the maxilla was fully corrected. The lower and lateral orbital border was well outlined. The exophthalmos was less conspicuous, and one year after the operation the exophthalmometric reading (Dr. Thomas Sanfacon) was 25 mm. for each eye. The hypertelorism became the most prominent factor in the facial appearance. The flatness and broadness of the nasal bridge and the increased distance between the medial poles of the eyebrows are factors which, by optical illusion, contribute to an apparent hypertelorism. In real hypertelorism these factors exaggerate the deformity.

Since the correction of this condition was not feasible, I attempted to minimize it by an indirect approach. On Feb. 19, 1951, a corrective rhinoplasty was performed, the nasal bridge being straightened and narrowed by a routine osteoplastic procedure. This effected considerable improvement in the facial appearance (Fig. 4*A* and *B*). Another procedure considered was advancing the eyebrows closer to the midline. However, the patient could obtain the same effect

Fig. 4.—*A* and *B*, postoperative appearance of the patient.

Fig. 5.—Apparent improvement of hypertelorism as a result of extending the eyebrows toward the midline. This effect is obscured by the uneven light effect around the eyes.

by judicious use of an eyebrow pencil (Fig. 5). A surgical procedure, therefore, did not seem warranted.

No attempt was made to correct the mild ptosis, since it was not functionally disabling and its correction would in all likelihood emphasize the exophthalmos. The over-all result of the two corrective operations was considerable improvement in the patient's facial appearance, as well as in her mental outlook.

SUMMARY

The facial deformity in acrocephaly is discussed, with emphasis on the abnormalities in facial appearance in its mild, subclinical forms. When this condition represents a severe cosmetic handicap, the indication for surgical improvement is apparent. The surgical procedures employed are based on an analysis of the deformity and are directed toward the improvement and minimizing of its prominent manifestations. An illustrative case is presented in which the recession of the maxilla was camouflaged by a chipped bone graft and the exophthalmos greatly improved. Various surgical procedures to minimize the effect of hypertelorism are discussed.

11 E. 68th St. (21).

Miss C. M. Dilinsky assisted in taking the photographs.

RELATION OF FACTORS INVOLVED IN MAINTENANCE OF OPTICAL PROPERTIES OF CORNEA TO CONTACT-LENS WEAR

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AMONG the problems confronting the use of contact lenses is the change in optical properties of the cornea which occurs when the conventional contact lens is worn. The effect of contact lenses on the physiology of the cornea is the subject of this communication.

When a conventional contact lens is worn, after a variable period the subject experiences development of a haze or mistiness in his vision (Sattler's veil) and sees colored halos or rainbows about light sources. These changes slowly disappear after the contact lens is removed. Since these optical phenomena are definite and subject to measurement, they were selected as the criteria in this study by which the effect of contact lenses on corneal function could be judged and measured.

There are many possibilities by which a contact lens might be expected to affect the cornea.

1. The type, shape, and point of contact of a lens with the eye is an obvious factor. Many variations of conventional lenses have been made, all of which apparently affect the optical qualities of the cornea to some degree. Dallos [1] reported in his experiments that a contact lens with the major part of the corneal segment removed did not affect the optical properties of the cornea. This experiment was repeated and confirmed in the present study, suggesting that the cause of corneal changes does not lie simply in the presence of a mechanical object causing minor irritation.

2. The composition of the contact-lens fluid has been considered widely as a major factor in the development of haze and halos (Obrig [2]). In experiments conducted in this laboratory, it was found that these fluids, varying in pH, buffering capacity, and osmotic pressure, all produced changes in optical qualities of the cornea of the same kind or degree (Finkelstein [3]). However, solutions of low osmotic pressure produced these changes earlier than did those of high osmotic pressure. The search for a contact-lens solution which would prevent development of the corneal changes presupposes that the solution placed in the lens remains there and that there is no appreciable drainage. Experiments concerned with this subject will be presented.

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From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons.

1. Dallos, J.: Sattler's Veil, Brit. J. Ophth. **30**:607, 1946.

2. Obrig, T. E.: Solutions Used with Contact Lenses, Arch. Ophth. **38**:668 (Nov.) 1947.

3. Finkelstein, I. S.: The Biophysics of Corneal Scatter and Diffraction of Light Induced by Contact Lenses, Thesis, Columbia University, 1951.

3. The osmotic pressure of the contact-lens solution is known to be an important factor in the maintenance of corneal transparency,[4] and studies of Cogan and Kinsey [5] on osmotic relations of the cornea provide a basis for a theoretical explanation of the corneal changes which occur when contact lenses are worn. According to these studies, the cornea is maintained in a state of deturgescence by the constant movement of water from the corneal stroma through the epithelium into the tear film, which is thought to be hypertonic to blood. An essential point in Cogan's hypothesis is that this water balance depends upon the existence of osmotic differences between the corneal film and the liquid phase in the cornea, with the epithelium serving as a semipermeable membrane, but not actively transferring water as a result of metabolic activity. If this movement or loss of water from the cornea should become reduced or should cease, the corneal stroma would become hydrated, and presumably thicker and turbid, and vision through it would be hazy. Data are available which strongly support the osmotic-pressure concept: (*a*) Clinical measurements by Kinsey [6] show that corneal thickness increases when a contact lens is worn. (*b*) Experiments (Smelser and Ozanics [7]) with guinea pigs show that water content, as well as turbidity, of the cornea increases when a contact lens is worn. (*c*) Furthermore, studies by Kinsey [6] on the osmotic pressure of the fluid worn under contact lenses demonstrate that the fluid rapidly becomes isotonic with blood serum, presumably by water passing into it from the cornea. (*d*) Finally, the studies of Finkelstein [3] show that it is the cornea which becomes more turbid, with the development of hazy vision noted subjectively when contact lenses are worn. Thus, the corneal haze may be explained. The halos seen when contact lenses are worn are relatively constant in diameter and appear to be diffraction phenomena which require, according to the calculations of Finkelstein,[3] that diffracting particles $16.1 \pm 0.2\ \mu$ in diameter be present in the cornea.

If, as the cornea becomes hydrated, the index of refraction of some elements becomes different from that of the surrounding substance, these elements would diffract light from their surfaces. This might well occur if all elements of the cornea did not hydrate to the same degree or at the same rate. The identity of such particles is unknown; but endothelial cells, some epithelial cells or their nuclei, and possibly spaces in the stroma between, or the surfaces of, the fiber bundles suggest themselves as possibilities.

4. Although the hypothesis here outlined seems to offer an explanation of the known changes in the cornea which are caused by wearing contact lenses, other possibilities should not be ignored. Among these is certainly that of the interference contact lenses must make with the gaseous exchange of the cornea and, therefore, with its metabolism. The cornea has a rather low oxygen requirement, owing to the great bulk of inert fibrous material, but it does require oxygen (Duane [8] and deRoetth [9]) and has been shown to use gaseous oxygen in vitro.[9] Whether it

4. Obrig.[2] Finkelstein.[3]

5. Cogan, D. G., and Kinsey, V. E.: The Cornea: V. Physiologic Aspects, Arch. Ophth. **28**:661 (Oct.) 1942.

6. Kinsey, V. E.: Personal communication to the author.

7. Smelser, G. K., and Ozanics, V.: Histology of the Guinea Pig Cornea as Affected by Contact Lens Wear, unpublished data.

8. Duane, T. D.: Metabolism of the Cornea, Arch. Ophth. **41**:736 (June) 1949.

9. deRoetth, A., Jr.: Respiration of the Cornea, Arch. Ophth. **44**:666 (Nov.) 1950.

utilizes atmospheric oxygen in vivo is unknown.[10] The osmotic-pressure concept does not require that the cornea use oxygen or expend energy in the removal of water from it to the exterior in order to maintain its optical properties.

The carbon dioxide produced by the cornea, if it could not escape readily through the tear film because of the presence of a contact lens, might so alter the pH that corneal transparency could be affected.

The present studies were planned to determine whether the osmotic concept outlined in paragraph 4 is an adequate explanation of the known facts and to evaluate the importance of gaseous exchange to corneal function in vivo.

EXPERIMENTAL INVESTIGATION

The studies reported here were carried out on four subjects—three volunteer students[11] and myself. Each subject was fitted with conventional contact lenses and with others designed for special purposes.[12]

I. *Tests on Rate of Drainage of Contact-Lens Solution.*—Presumably, some exchange of the fluid under a contact lens with the tears and fluid in the conjunctival sac takes place mechanically. The rate of this exchange probably varies with the closeness of the mechanical fit of the lens to the globe, but, according to the studies of Cogan and Kinsey,[5] water would leave the cornea and dilute a hypertonic contact-lens fluid until the solution became isotonic with blood. If a solution of fluorescein were placed under the lens, its concentration should decrease in time, partly as a result of mechanical drainage and partly owing to the inflow of water from the cornea. The drainage rate of the fluorescein should be markedly affected by the osmotic pressure of the contact-lens solution, being greater from a hypertonic solution and much less from an isotonic or a hypotonic one.

This hypothesis was tested by use of a special lens (Fig. 1), equipped with an inlet and outlet which could be closed, or fitted with an adapter which would allow the lens solution to be withdrawn into a syringe and the dye content subsequently determined in a photometer. The contact-lens solution obtained in this way was not contaminated to any practical degree with the contents of the conjunctival sac. These lenses were fitted to each of the four subjects and worn with a solution containing 5 mg. of sodium fluorescein per 100 cc., made up in 1.3, 2.0, and 2.6% sodium bicarbonate solutions. The 1.3% solution is about isotonic, or very slightly hypotonic. The solution ordinarily used for contact-lens wear is 1.5 to 2.0% sodium bicarbonate or its equivalent in osmotic pressure. The fluorescein solutions were worn for periods of 15, 30, 45, and 60 minutes; the lens solution was withdrawn, and the fluorescein content was determined. The results are shown in Figure 2. A rapid loss of fluorescein was found to occur from the solutions of higher osmotic pressure during the first 15- to 30-minutes' wear. After this initial loss, drainage of fluorescein proceeded at a very low rate, probably representing only mechanical drainage, the outflow of water from the cornea having become greatly reduced.

10. (*a*) Bakker, A.: Some Researches on the Respiration of the Cornea in Albino Rats, Brit. J. Ophth. **31**:100, 1947. (*b*) Fischer, F. P.: Über den Gasaustausch der Hornhaut mit der Luft, Arch. Augenh. **102**:146, 1930.

11. Bruce Wild, Bradford Wild, and Frank Weinert, students at the School of Optometry, Columbia University, served as volunteer subjects in this study.

12. The special contact lenses were made in the Obrig Laboratories, Inc., New York, and fitted by Mrs. Margaret Bergman, of that company.

The drainage rate was related to the osmotic pressure of the fluorescein solution, for it was greatest for the 2.6% sodium bicarbonate solution, intermediate for the 2.0% solution, and practically zero for the 1.3% solution. Some variation was noted in the drainage rate in the same subject from day to day, and an even

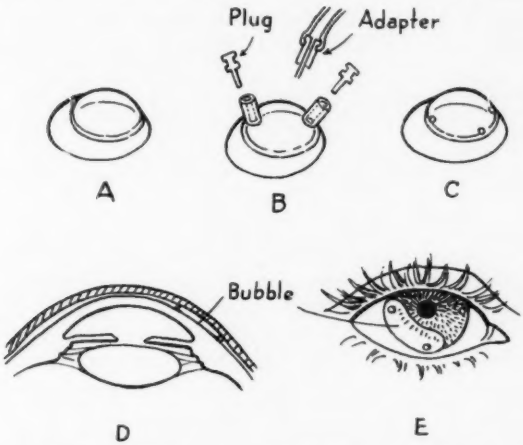

Fig. 1.—Various types of contact lenses used in the experiments. *A*, conventional lens; *B*, irrigation lens; *C*, ventilated lens. *D*, shows relation of ventilated lens to eye; *E*, appearance of ventilated lens and air space.

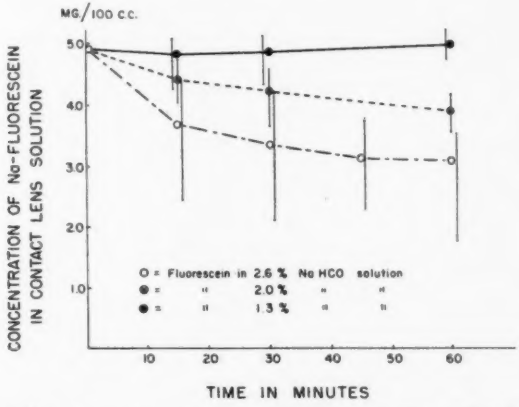

Fig. 2.—Relation of osmotic pressure to drainage rate of the contact-lens solution.

greater difference between subjects. One subject consistently had a rapid drainage; another, a very slow one. Variations in fit of the lens appear to explain this. The degree of variation is indicated in the graph (Fig. 2).

II. *Effect of Various Concentrations of Sodium Bicarbonate Solutions on Cornea as Judged by Halo Development.*—According to the concept that corneal

changes caused by contact lenses result from the loss of a hypertonic precorneal film, it follows that the same corneal changes would occur if the eye were bathed in hypotonic solutions when no contact lens was worn. For this purpose, diving goggles [13] were worn, acting as reservoirs in which each eye was kept submerged in from 15 to 20 cc. of solution.

It was found that brilliantly colored halos developed within four minutes when distilled water bathed the cornea. Dilute solutions of sodium bicarbonate—0.125, 0.25, 0.3, and 1.0%—also produced halos when worn in goggles and without contact lenses. In addition to these halos, vision became hazy, as it does with contact lenses. A longer time was required to produce halos when higher concentrations of sodium bicarbonate were used. However, when goggles containing a 1.3% solution were worn, halos were not obtained after the eye had been immersed for two hours.

The halos produced by goggles and hypotonic solutions were as bright as those seen with contact lenses and had the same angular diameters. It is quite certain, therefore, that the phenomenon here produced by hypotonic solutions is the same as that occurring when contact lenses are worn.

The time required for the development of halos for a given subject, lens, and solution is remarkably constant. Four subjects fitted with conventional lenses worn with a 1.5% solution of sodium bicarbonate reported the appearance of halos within an average of 115 minutes after the contact lenses were inserted. When this experiment was repeated, the average for nine observations was 114 minutes. These tests were made with a standard light source in a dark room.

In addition to the time required for the development of halos, their brightness could be quantitatively determined. This was done with an apparatus devised in this laboratory by Dr. Finkelstein,[3] who was working on other phases of the problem. Details of construction are given elsewhere [3]; however, the apparatus consisted of a brilliant green light source (a mercury-vapor lamp equipped with filters to isolate the green band), the light passing through a primary 1.5-mm. aperture. Halos produced by a hypotonic solution used as an eye bath or by wearing contact lenses would be perceived as a green ring surrounding this light source. Contiguous with this halo was arranged for comparison an arc illuminated by the same source as the primary aperture. The brightness of the second arc could be controlled by the subject. In this way the brightness of the halos could be determined by comparing them with a similar adjacent field (Fig. 3). The photometric measurement was monocular and monochromatic, and, according to Finkelstein's data, matching could be made with an accuracy of 5%.

The volume of fluid contained in the contact lenses should affect the time required for the development of halos, according to the osmotic-pressure concept, for a longer time would be required for a larger volume of hypertonic solution to be reduced to isotonicity than for a smaller one. Accordingly, lenses differing considerably in the volume of fluid contained in them were fitted to the right and left eyes of the four subjects. These were a conventional small-volume lens and a large-volume lens, the same as that used in the drainage experiment (Fig. 1*B*). The apical corneal clearances were about 0.5 and 1.5 mm., respectively. It was found that when these lenses were worn halos developed slightly later from the

13. Cover's gas-tight "nod-and-shake" rubber goggles.

large-volume lens (Fig. 4) than they did from the small-volume lens. This finding was consistent, with no exceptions in a large series of comparisons. However, as may be noted in Figure 4, the halos which arose later with the large-volume lenses became far brighter than did those produced with small-volume lenses. The fact that the large-volume lens was equipped with inlet-outlet connections is not thought to be responsible for the differences in behavior of the lens, for a large-volume lens similar to the others save for these attachments gave the same results, as shown in Figure 4.

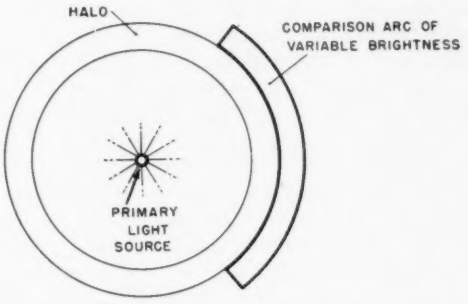

Fig. 3.—Measurement of halo caused by wearing a contact lens.

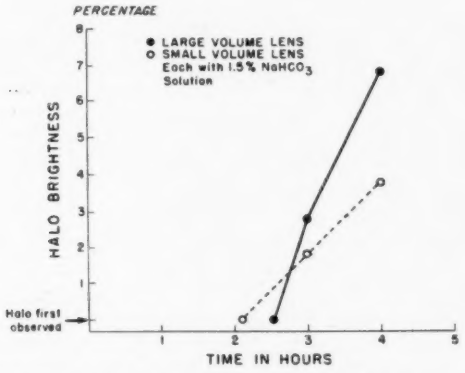

Fig. 4.—Effect of volume of the contact lens on development of halos.

If a contact lens could be worn with a provision for constant maintenance of the osmotic pressure of the solution, no halo should develop, according to the requirements of the osmotic concept of the mechanism of this phenomenon. This condition can be attained by the use of irrigation lenses (Fig. 1*B*), by means of which the contact-lens solutions can be changed periodically without removal of the lenses. Halos developed regularly in all four subjects when these lenses were worn with a 2% sodium bicarbonate solution.

According to the data obtained by Kinsey,[6] the drop in osmotic pressure in a contact lens takes place very rapidly, reaching nearly the critical isotonic level in 15

to 30 minutes. Therefore, the fluid was replaced every 15 minutes in the irrigation lenses by connecting one outlet of the lens with a burette containing the solution. Approximately 5 to 10 cc. of fluid was used at each irrigation. The experiment was continued for 7¼ hours with all four subjects. No halos or haze developed in any case, whereas with the same lenses and subjects, and with the same solution allowed to remain unchanged in the lenses, bright halos were present in an average of 2 hours 40 minutes. The frequent changing of the solution certainly provided more mechanical trauma to the eye than would normally occur, and there was more hyperemia than usually occurred when this contact lens was worn. This experiment clearly demonstrates that a contact lens can be worn much longer without development of halos or haze if the osmotic pressure of the solution is maintained. However, factors other than osmotic pressure were also varied in this experiment. Waste products of corneal metabolism or carbon dioxide which might have accumulated in the contact-lens fluid were removed, and a fresh supply of dissolved oxygen was made available to the cornea. For this reason, the possible role of gaseous exchange in the development of halos was investigated.

III. *Effect of Atmospheric Oxygen and Carbon Dioxide on Optical Properties of the Cornea.*—Rubber goggles were fitted with a rubber inlet and outlet tube, so that the eye could be maintained in various atmospheres by passing gases from pressure tanks through the right goggle, over the bridge of the nose to the left goggle, and out through a second tube, the end of which was immersed in 1 or 2 cm. of water. The gases were passed through the goggles at low pressure continuously for a four-hour test period. The flow of gas could be demonstrated by the bubbling at the end of the outlet tube or by evidence of its flow at its entrance into the right goggle. The flow was arranged to be continuous and under some pressure to insure that the eye was at all times in a known experimental atmosphere. There was undoubtedly some leakage under the edge of these rather tight and well-fitted goggles, but the flow was from within out, and we feel confident that there was no contamination of the experimental gas with air. Of course, no contact lenses were worn in any of these experiments.

The first atmosphere tested was air saturated with water vapor by passing compressed air through a gas-washing bottle containing distilled water, maintained thermostatically at a temperature of from 41 to 42 C. About 2 cc. of distilled water was placed in each goggle at the beginning of the experiment, and as the warm saturated air from the washing bottle entered the goggle, condensation took place on the inner surface of the goggle lens. By this means the cornea was maintained in an atmosphere with normal components of oxygen, nitrogen, and carbon dioxide, but evaporation from the tear film was minimal. Actually, the osmotic pressure of the tear film tended to become reduced because of the large area of distilled water contained in the goggle. According to the reports of Cogan and Kinsey,[5] movement of water from the cornea to the tear film is due to the hypertonic character of that film. It was presumed that the tears on the cornea were hypertonic as elaborated by the lacrimal gland, or became so by evaporation from the corneal surface. Both these processes may be operating under normal conditions, but in the present experiments evaporation was not a factor.

Maintenance of the eye in a moist atmosphere for four hours did not produce halos in any of the four subjects (Table 1). This test was repeated in two instances, with the same results.

In a second experiment, carried out in the same manner as the foregoing one, it was endeavored to determine the effect of excluding atmospheric oxygen from the cornea. For this purpose, nitrogen from a cylinder was passed first through a wash bottle containing Fieser solution,[14] in order to remove any traces of oxygen, and then through a second gas-washing bottle containing water, thus preventing any droplets of the Fieser solution from coming in contact with the eye. In one experiment the second wash bottle was kept cold, and no water was placed in the goggles, so that the cornea was in a relatively dry, oxygen-free atmosphere. The experiment was run for four hours, and conditions of pressure and gas flow were as before.

Three subjects were tested under these conditions, and all reported colored halos at the conclusion of the four-hour period (Table 1). These halos, though definite, were faint, and gave minimal readings on the halometer.

The third series of experiments was conducted in the same manner on four subjects, except that distilled water was placed in each goggle and the water in the gas-washing bottle was maintained at 41 to 42 C., as in the experiment with moist

TABLE 1.—*Effect of Atmospheric Water Vapor, Oxygen, Nitrogen, and Carbon Dioxide on Development of Colored Halos*

Gas	Brightness of Halos (%) at 4 Hr.		No. of Subjects
	O. S.	O. D.	
Air saturated with water vapor	No halos	No halos	4
Relatively dry nitrogen	.....	0.06%	4
Nitrogen saturated with water vapor	0.89%	0.75%	4
Nitrogen (85%) and CO_2 (15%) saturated with water vapor	0.92%	0.70%	4
Air (85%) and CO_2 (15%) saturated with water vapor	No halos	No halos	4

air. All four subjects reported bright halos at the conclusion of the four-hour run (Table 1). These halos were seen in two cases within three hours. Observations were not made earlier, or at all, in the other two cases, because clear vision through the condensate on the inner surface of the goggles was not possible. Vision also became somewhat misty in these experiments, as was noticed when the goggles were removed.

The angular size of the halos produced by an oxygen-free atmosphere was the same as that of the halos caused by contact lenses, indicating that one was concerned with essentially the same phenomenon. Although care was taken to keep the cornea in an oxygen-free environment, this was obviously not strictly possible. The tears undoubtedly contain some oxygen, possibly in a concentration similar to that found in blood serum. This oxygen would be lost, however, from the tear film to the nitrogen gas over it, as well as to the corneal epithelium beneath it.

A fourth experiment was conducted with the purpose of determining whether or not the presence of carbon dioxide affected the development of the corneal changes. In the preceding experiment any carbon dioxide produced by the cornea would have been carried away by the stream of nitrogen. To test this, a gas mixture of 85% nitrogen and 15% carbon dioxide was obtained. This mixture was passed

14. Sodium hydrosulfite is dissolved in alkali, and a small amount of sodium anthraquinone-β-sulfonate is added. The water-soluble quinone is reduced to a blood-red vat, being left with a great affinity for oxygen.

through a gas-washing bottle containing water at from 41 to 42 C. and to the goggles, as in the preceding experiment. This carbon-dioxide concentration caused a smarting or stinging sensation in the eyes, which gradually subsided. The gas was not passed through Fieser's solution because of its effect on the carbon dioxide.

Bright halos were produced in all four subjects (Table 1), and haze or misty vision was also noted. Again, the halo diameter gave evidence that the diffracting bodies were the same as those causing the contact-lens halos. The halos were noted as early as two to three hours by all four subjects, but, again, condensation on the inner surface of the goggles prevented good observations at frequent intervals. The halos certainly appeared earlier than at three hours. The halos caused by the nitrogen-carbon dioxide mixture were about as bright as those caused by nitrogen alone, giving no evidence that high carbon-dioxide concentration accentuates the processes leading to halo formation.

The fifth experiment in this series was made with a mixture of 85% air and 15% carbon dioxide. In the preceding experiment the halos were presumably caused by the absence of oxygen. In the present experiment a high carbon-dioxide content

TABLE 2.—*Effect of Oxygen, Nitrogen, and Carbon Dioxide in Contact-Lens Fluid on Halo Development*

	No. of Tests	No. of Subjects	Halo Brightness (%)		Time of Halo Appearance, Min.
			3 Hr.	4 Hr.	
Nitrogen *	11	4	3.0	5.5	140
Oxygen *	14	4	0.0	0.16	Up to 435
Control (no gas added)	9	4	2.9	6.9	139
Carbon dioxide	4	4	3.3	6.3	122

* Bubbles of gas were present in the contact-lens fluid (1.5% sodium bicarbonate solution).

of the atmosphere was provided to test whether an excess of that substance would affect the optical properties of the cornea. The experiment was conducted as before, except that the temperature of the water in the gas-washing bottle was raised to approximately 50 C. in order to insure that the gas passing through the goggles should contain a maximum quantity of water vapor.

The air-carbon-dioxide mixture did not cause the formation of halos in any of the four subjects, and they noted no haze in their vision. The experimental period was four hours, as before. These data strongly indicate that high concentration of carbon dioxide does not cause the corneal changes found when contact lenses are worn.

IV. *Effect of Oxygen, Nitrogen, and Carbon-Dioxide Content of Contact-Lens Fluid on Development of Halos.*—An attempt was made to apply the result of the experiments on the effects of various gases on the corneal halos to the halo produced by wearing contact lenses. For this purpose, the irrigation lenses (Fig. 1*B*) were again worn by the four subjects. A solution of 1.5% sodium bicarbonate was washed with oxygen-free nitrogen and introduced through the inlet tube. At the beginning of the experiment a nitrogen bubble was also introduced into the lens through one of the inlet tubes. The nitrogen gas had been washed through Fieser's solution, and was collected and introduced into the lens in such a manner that no contamination with air occurred. The bubbles of nitrogen were from 3.5 to 4.0 mm.

in diameter in one series of experiments and about 9.0 mm. in another. Three series of experiments were run with all four subjects.

The time required for halos to develop and the brightness they attained in three to four hours after insertion of the lens were determined. Addition of nitrogen bubbles had no significant effect on the time required for the development of halos or on their brightness.

In the second series of tests, bubbles of oxygen were introduced into the contact lenses at the beginning of the experiments, and at intervals a lens inlet tube was opened and fresh oxygen introduced into the bubble. This was accomplished with the aid of a hypodermic syringe filled with oxygen, which was forced into the bubble through a narrow-gauge needle. This procedure was intended to wash out any carbon dioxide and to replace it with fresh oxygen. This renewal of the oxygen supply was done at 20-, 30-, and 40-minute periods in different experiments, all with the same results. Since repeated opening of the lens and introduction of fresh oxygen led to loss of contact-lens fluid, one series of experiments was performed in which a rather large bubble of oxygen, about 8.0 mm. in diameter, was introduced at the beginning of the experiment, and no subsequent changes were made.

No halos developed in any of the four subjects as long as oxygen in the bubbles was replaced from time to time, and hazy vision was not noted subjectively. When one large bubble of oxygen was introduced at the beginning of the experiment, it became steadily smaller, presumably as the oxygen was utilized by the cornea. Halos finally appeared from four to five hours after the contact lens had been inserted, whereas they were first seen ordinarily after 2½ hours. In the first of these oxygen experiments the periodic replacement of oxygen also allowed any accumulated carbon dioxide to escape. In the last experiment carbon dioxide was retained.

Since the foregoing experiment suggests that no haze or halos develop as long as an adequate oxygen supply is maintained in the lens, it appeared desirable to test this observation more exactly in a longer experiment. Therefore the same lenses were worn with a 1.5% sodium bicarbonate solution by three of the subjects. A large oxygen bubble was introduced at the beginning of the experiment, and after three and six hours the oxygen in the bubble was renewed. These large oxygen bubbles steadily decreased in diameter, indicating that oxygen was being removed. No haze or halos developed during the 7¼ hours of the test in three experiments, whereas in control experiments with the same lens and solution halos were very evident in 2½ hours. In one experiment the oxygen bubble was removed at the third hour, but no second renewal was made. Halos appeared in this case seven hours after insertion of the lens. In a fifth experiment, the final oxygen bubble introduced into the lens was rather small, and, although no halos were observed while the lens was worn, faint ones were detectable upon its removal, after 7¼ hours. These halos faded rapidly and disappeared in 20 minutes.

In the next series the effect of carbon dioxide on halo development was studied. The irrigation contact lenses were worn by the four subjects with the introduction of a 1.5% sodium bicarbonate solution from a burette in which it was in equilibrium, at room temperature, with a gas mixture of 85% nitrogen and 15% carbon dioxide. The pH of this solution was reduced a few tenths of a pH unit by the carbon dioxide. The fluid caused a slight stinging sensation, which soon disappeared. The addition of carbon dioxide to the contact-lens solution did not appreciably affect the time

required for development of halos, or their brightness, three and four hours after the lens was inserted.

V. *Effect of Ventilation of Contact Lenses on Halo Development.*—The results of the experiments reported above suggest that contact lenses could be worn for greater periods should the cornea have an adequate oxygen supply. This conclusion was tested by devising a contact lens made from the same mold as the others used in these experiments, but with the central portion separated from the cornea only by a capillary space over the pupil filled with the precorneal tear film, so that an optically useful lens resulted. A large, usually crescentic, bubble surrounded the pupillary zone. This was displaced with movements of the eye, so that, according to the direction of the gaze, it covered at various times the entire cornea, save the central region. This bubble was exposed to the outside by means of three holes, 1.6 mm. in diameter, placed as indicated in Figure 1*C*, so that it would at all times be freely open to the exterior. Slight movements of the lens relative to the eye, caused by changes in the direction of the gaze, constituted a pumping mechanism, it was thought, which would aid in mechanically changing the gas content of the bubble. Diffusion of air through three holes of this diameter should be rapid. These lenses were fitted with the usual care given the fitting of conventional lenses.

Three of the subjects were fitted and wore these lenses on one eye, while, as a control, a conventional lens with 1.5% sodium bicarbonate solution was worn on the other. One subject was tested on three occasions, while experiments on the other two were conducted on four separate days. On each occasion the lenses were worn for seven hours. In eight of these experiments the lenses were worn for seven hours without the appearance of halos or noticeable haze. In the other experiments faint halos were observed by each subject. On one occasion faint halos were noted, which subsequently faded away while the lenses were still being worn. These halos were just noticeable 3¼ hours after insertion of the lens, whereas the halos of conventional lenses worn as controls at the same time appeared in less than 2¼ hours. The data obtained in this experiment are plotted in Figure 5. An additional control experiment was carried out by filling the perforations with paraffin and wearing the lenses with 1.5% sodium bicarbonate solution, as were the conventional lenses. When the perforations were closed in this manner, halos appeared very quickly, and the lenses were extremely uncomfortable, and therefore removed.

Although these lenses suffered from disadvantages which would not recommend them for regular use, they demonstrated that providing the cornea with access to the atmosphere either delayed or minimized the development of haze and halos or prevented their appearance entirely.

VI. *Effect of Pressure on Brightness of Contact-Lens-Halos.*—One factor by which contact lenses might affect the eye and the halos which are produced is the mechanical pressure which they may exert on the globe. The lids may be expected to exert greater pressure when the lenses are large or when the subject is unaccustomed to them and involuntary contraction of the orbicularis occurs. The last reaction has often been assumed to explain the increasing tolerance which is noted as lenses continue to be worn. Experiments cited by Dallos [1] have indicated that wearing time could be increased by orbicularis anesthesia. Figure 4 shows that the halos produced by a large, bulky lens were brighter than those produced by a shallower lens. An attempt was made to determine whether mechanical pressure could cause such a difference in halo brightness.

The conventional lens was worn with 1.5% sodium bicarbonate solution until halos were well developed. A standard pressure bandage was then placed over the eye,[15] so that it was subjected to definitely more than normal pressure for 20 minutes, when the bandage was removed and the halos were measured. The pressure was not reapplied, but the halo brightness was again determined. The results of

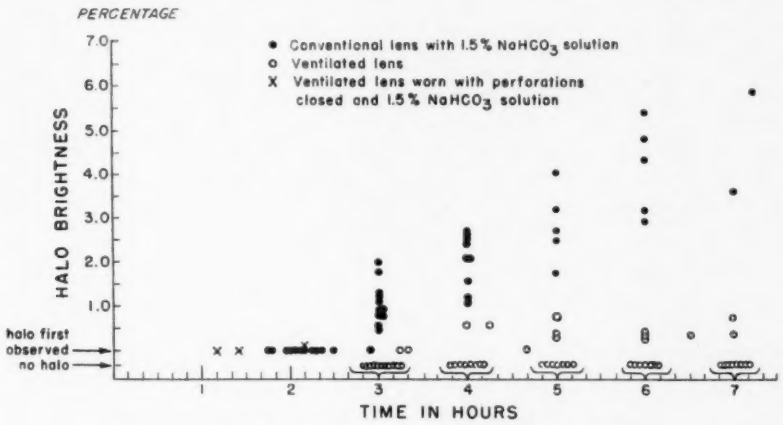

Fig. 5.—Effect of ventilation of a contact lens on halo brightness.

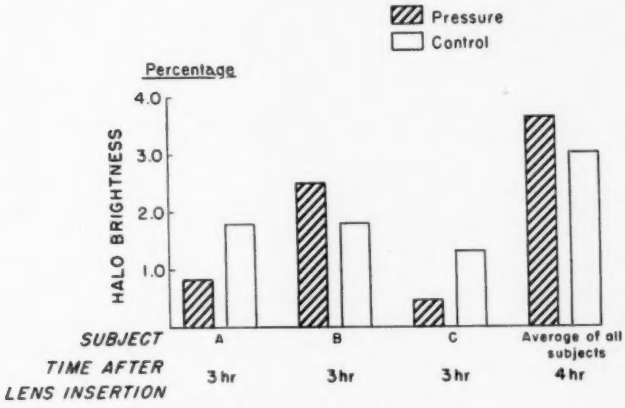

Fig. 6.—Effect of pressure on halo brightness.

these tests, repeated three times on each of three subjects, are given in Figure 6. In every experiment performed on two of the subjects halo brightness was less after the application of pressure, but in the third this reaction did not occur in two of the three tests. For this reason, the results on each subject are plotted separately.

15. These experiments were conducted under the supervision of Dr. John P. Macnie, Institute of Ophthalmology, Columbia University.

After removal of the pressure bandage the halos rapidly increased in brightness until they became even slightly brighter than in the controls.

VII. *Changes in pH of Solution Under the Contact Lens.*—Although halos were not produced by exposing the cornea to atmospheres containing 15% carbon dioxide, and addition of carbon dioxide to the contact-lens solution had no effect on the kinetics of halo production, it still remained of interest to determine whether any change takes place in the pH of the solution as it is worn under the contact lens. Recourse was again had to the irrigation lens, from which the contact-lens solution could be removed without contamination with either tears or air. A capillary glass electrode was used (Beckman No. 290-M), in which the glass membrane is in the form of a capillary tube with a capacity of about 0.01 ml. To make a determination, the electrode tip was inserted into the contact lens through one of the outlet tubes and the fluid drawn through the capillary. The electrode was flushed three times in this manner and the pH of the solution then determined. The fluid entered the

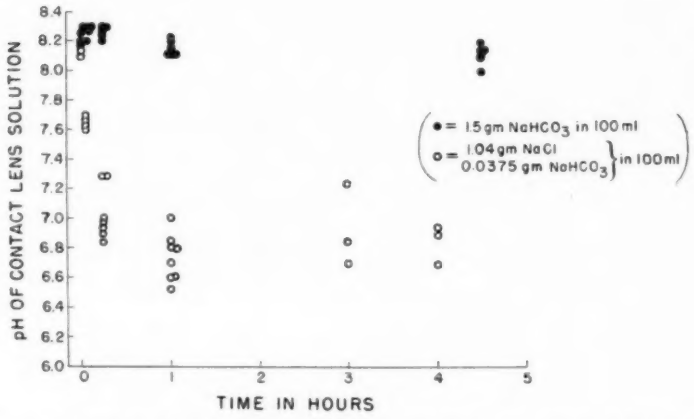

Fig. 7.—Change in pH of the solution during contact lens wear. The high values for the sodium chloride solution at one, three, and four hours were all obtained from the same subject.

electrode assembly directly from the contact lens without exposure to air. The electrode was checked against three standard buffers prior to and after each experiment.

All four subjects were used in this experiment, and the changes in pH of the two solutions were tested. A 1.5% solution of sodium bicarbonate, which has considerable buffering capacity, and a 1.04% solution of sodium chloride adjusted to about pH 8.1 by the addition of 0.0375 gm. of sodium bicarbonate per 100 ml. were used. These two solutions were essentially isotonic and of the same initial pH, but differed markedly in buffering capacity. The data obtained in these experiments are shown in Figure 7. The pH of the 1.5% sodium bicarbonate solution changed slightly, even in 4¼ hours. The pH of the weakly buffered solution, however, decreased rapidly after the lens was inserted. It fell below pH 7.0 in 15 minutes but remained fairly stable at pH 6.6 to 7.2 after one, three, and four hours' wear. The highest pH values in all these tests were obtained from the same subject.

Of considerable interest in these experiments was the development of halos at an unusually early time when the sodium chloride solution was used. Halos were

observed within 40 minutes after insertion of the lens with this solution. These halos were transient in some cases, fading, and then returning at the time of their usual development. Their average diameter ranged from 2 degrees 48 minutes to 3 degrees no minutes. Since the two solutions were essentially isotonic, it is difficult to explain these results on the basis of an osmotic-pressure relation alone. The factor responsible for the decrease in pH of the lens solution is unknown. Carbon dioxide and lactic acid suggest themselves as probable agents.

COMMENT

The interference of contact lenses with the optical properties of the cornea appears to be due to the disruption they cause in the normal water-removal mechanism. The osmotic relation between the cornea and a hypertonic tear film would undoubtedly aid in maintaining the cornea in a partially deturgesced state, but it does not appear to be the only mechanism involved. In addition, the present experiments show that the cornea possesses a means for the removal of water from itself which requires atmospheric oxygen. It has not been demonstrated which corneal elements are engaged in this activity, but because atmospheric oxygen is required the epithelium is suspect. The reports of Bakker [10a] and Fischer [10b] are interesting in this connection, although these investigators were handicapped by difficulty in observing corneal changes in animal eyes. The present data are not in agreement with those of Bakker, who reported that atmospheric oxygen was not required by the cornea. One may, however, agree with his conclusion that carbon dioxide in a concentration of 8% in atmosphere had no effect on corneal structure.

The exact mechanism of water removal from the cornea which is utilized in this process is unknown. As was pointed out by Maurice,[16] the excretion of water itself would be inefficient, for it would immediately tend to diffuse back into the cornea. According to this author, the cornea may actively transfer some ion, such as Na, into either the aqueous humor or the tear film, thus providing a more efficient mechanism for water removal. Lactate ions are particularly suited to this role. The data reported by Davson [17] appear to be in agreement with this concept.

The results in some of the experiments, described above, support the osmotic-pressure concept of water removal from the cornea but do not exclude other mechanisms. The slight delay in the appearance of halos when larger-volume contact lenses are worn is one bit of evidence, and the direct relation of the osmotic pressure of contact-lens fluid to the rate of drainage is another. In the experiment in which the contact-lens fluid was frequently renewed, not only was a hypertonic precorneal medium maintained, but additional oxygen was also provided with each change. When perforated lenses were used, they not only permitted an interchange of a presumably hypertonic tear fluid, since they did not become tightly fixed to the eye, but, in addition, allowed the cornea access to atmospheric oxygen. Therefore these experiments do not exclusively support the osmotic-pressure concept, since the results could also be due to the additional oxygen supplied.

The results of other experiments, however, cannot be explained on the basis of osmotic-pressure relation. A 1.3% sodium bicarbonate solution is slightly hypo-

16. Maurice, D. M.: The Permeability to Sodium Ions of the Living Rabbit's Cornea, J. Physiol. **112**:367, 1951.

17. Davson, H.: Some Considerations on the Salt Content of Fresh and Old Ox Corneae, Brit. J. Ophth. **33**:175, 1949.

tonic; yet when the eye was immersed in a considerable volume of such a solution, halos did not appear. On a purely osmotic basis, the cornea should have become hydrated. It is suggested that under the conditions of this experiment the elements of the cornea actively secreted enough water to maintain its normally deturgesced state. When extremely hypotonic solutions were used, water entered the cornea from the bath, and this secretory or active-transfer mechanism was not able to cope with its removal, in addition to that normally expelled.

Some of the experiments of Finkelstein [3] appear to illustrate this point. Contact-lens solutions of low osmotic pressure (0.125 and 0.25% sodium bicarbonate) produced early and intense corneal haze, whereas the corneal haze produced when more nearly isotonic solutions (0.5, 1.0, and 1.5% sodium bicarbonate) were used was less extreme and occurred after a longer period of lens wear. There appeared, therefore, to be a decided difference in the behavior of the cornea to these two groups of solutions, rather than a regular gradation in their effect proportional to their osmotic pressure. It is possible that the metabolic mechanism was quite inadequate to maintain a state of deturgescence of the cornea exposed to the extremely hypotonic medium, so that it became hydrated, thicker, and turbid. When solutions approaching isotonicity with blood serum were used, the metabolic processes were then able to maintain a fairly normal condition in the cornea, since excessive quantities of water did not enter the cornea from a hypotonic contact-lens fluid.

Maintenance of the cornea under relatively anaerobic conditions produced some visual haze and halos, the latter being apparently identical with those caused by contact lenses. This was not caused by changing the osmotic relation between the cornea and the tear film. Possibly the use of moist nitrogen reduced evaporation from the precorneal film, thus making it less hypertonic than normal; but halos were not produced by air or air-carbon dioxide mixtures saturated with water vapor, which also reduced evaporation. Drying of the precorneal tear film probably plays a role in the mechanism of water removal from the cornea, since halos produced by relatively dry nitrogen were not as bright as those produced in a moist atmosphere. Presumably, the dry gas increased the osmotic pressure of the tear film by evaporation, which aided in the abstraction of the water.

The demonstration that addition of an adequate oxygen supply, by means of oxygen bubbles to the contact-lens fluid, prevented the development of halos clearly indicates that factors other than osmotic pressure are involved. In these experiments the osmotic pressure of the contact-lens solution was not modified directly, but oxygen was provided, which enabled the cornea to maintain its optical properties.

Factors other than metabolic and osmotic relations may affect the development of halos, but they do not seem to be of prime importance. When well-buffered contact-lens solutions are used, the halos develop without an appreciable change in pH of the solution under the lens. However, if the solution used is very poorly buffered, the pH decreases rapidly and halos are seen more quickly. The cause of these rapidly developing halos is not clear, but the solutions used were isotonic with the more highly buffered sodium bicarbonate solutions with which halos developed more slowly. Other experiments, in which the cornea was exposed to high concentrations of carbon dioxide in the atmosphere, did not result in the production of halos.

Physical pressure of the contact lens on the globe undoubtedly is an important factor in the comfort of such lenses, but the pressure itself does not seem to be

directly responsible for halos. Added pressure on the lens and eye did not make the halos more intense, and oxygen bubbles, which prevented halos, presumably did not affect the pressure of the lens on the eye more than the nitrogen bubbles did.

SUMMARY

The foregoing studies lead to the suggestion that contact lenses interfere with the optical properties of the cornea by affecting the water balance of that tissue. The cornea is a very hydrophilic structure, which must constantly be kept in a state of partial deturgescence in order that its normal optical properties may be maintained. This is accomplished by (1) a hypertonic precorneal tear film, which removes water from the cornea, through the osmotic forces involved, and (2) the metabolic activity of some corneal cells, which actively transfer water or salts from the cornea, requiring oxygen and metabolites and expending energy to do so. The hydration of the cornea accounts for its increase in thickness and turbidity, and differential hydration of various corneal components (cells, nuclei, fibers, or interstitial ground substance) forms a hypothetical basis for the diffraction phenomena (halos).

Conventional contact lenses become very tightly fitted to the eye, preventing both the maintenance of a hypertonic precorneal film and access of oxygen to the corneal surface. Changes in the optical properties of the cornea associated with conventional contact lenses should be, and are, much less or minimal when lenses are worn which, because of perforations or other means, such as those in corneal lenses, permit (1) rapid exchange of tears with the fluid under the lens and (2) adequate access of the cornea to oxygen.

CONCLUSIONS

The drainage rate of the fluid under a contact lens is affected by the osmotic pressure of the fluid.

Halos of contact-lens type are produced, without contact lenses, in as short a time as four minutes by bathing the eye in hypotonic solutions. A longer period is required when solutions of greater osmotic pressure are used.

If the contact-lens fluid is replaced at frequent intervals, thus maintaining a hypertonic medium under the lens, "halos" do not appear.

Halos, similar to those caused by contact lenses, occur when the eye is exposed to an atmosphere of nitrogen. A 15% concentration of carbon dioxide in the nitrogen does not affect the development of the halos, and 15% carbon dioxide in air does not cause halos in such experiments.

The presence of oxygen bubbles under a contact lens, worn with a 1.5% sodium bicarbonate solution, prevents the development of halos.

Lenses which allow access of the cornea to the atmosphere can be worn for long periods without the development of halos.

The pH of a well-buffered contact-lens solution remains quite constant under the lens, but the pH of a poorly buffered solution becomes acid within a few minutes of lens wear. Halos appear early when poorly buffered solutions are used.

It is concluded that deturgescence and the optical properties of the cornea are maintained by metabolic activity of the cornea, which requires atmospheric oxygen. The presence of a hypertonic precorneal film would aid in this process. Ordinary contact lenses interfere with these mechanisms.

STUDIES ON THE INTRAOCULAR PENETRATION AND TOXICITY OF TERRAMYCIN

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TERRAMYCIN, an antibiotic with a broad antibacterial spectrum, is an elaboration product of the actinomycete Streptomyces rimosus.[1] Investigators[2] have reported on the effectiveness of terramycin in the treatment of bacterial, viral, rickettsial, and protozoan diseases. Welch and associates[3] have reported on the absorption, distribution, and excretion of this antibiotic after systemic administration to man and the experimental animal. The toxic properties have been investigated by Schoenbach, Bryer, and Long.[4] The present study was undertaken to evaluate the penetrability of terramycin into the ocular fluids and tissues after local and systemic administration. Additional experiments were devised to study the toxic effects of terramycin on ocular tissues. Since this study was undertaken, reports on the intraocular penetration of terramycin and its clinical effectiveness have appeared.[5]

GENERAL PROCEDURE

Local Administration.—Solutions: Drops of terramycin hydrochloride in aqueous solution in concentrations of 5 and 25 mg. per cubic centimeter were instilled into 48 rabbit eyes every five minutes for six doses. After the instillation of two drops of 0.5% tetracaine hydrochloride,

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From the Research Laboratories of the Wills Hospital and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine.

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2. Finland, M.; Gocke, T. M.; Jackson, G. G.; Womack, C. R., and Kass, E. H.: Clinical Studies on Terramycin, Ann. New York Acad. Sc. **53**:290, 1950. Hobby, G. L.; Dougherty, N.; Lenert, T. F.; Hudders, E., and Kiseluk, M.: Antimicrobial Action of Terramycin in Vitro and in Vivo, Proc. Soc. Exper. Biol. & Med. **73**:503, 1950.

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5. Douvas, N. G.; Featherstone, R. M., and Braley, A. E.: Role of Terramycin in Ophthalmology, A. M. A. Arch. Ophth. **46**:57 (July) 1951. Town, A. E.: Ophthalmic Use of Terramycin, Am. J. Ophth. **34**:723, 1951. Thygeson, P.: Terramycin in Ocular Infections, presented at the 87th Annual Meeting of the American Ophthalmological Society, White Sulphur Springs, W. Va., June 7-9, 1951. Mitsui, Y., and others: Terramycin in the Treatment of Trachoma, A. M. A. Arch. Ophth. **46**:235 (Sept.) 1951.

0.05 cc. of terramycin hydrochloride in a concentration of 50 mg. per cubic centimeter was injected subconjunctivally into six rabbit eyes.

Ointments: Terramycin hydrochloride in concentrations of 1 and 30 mg. per gram of base was applied to 48 rabbit eyes, the eyes of normal rabbits only being used. In all eyes that received terramycin topically, the cul-de-sacs were thoroughly washed with sterile isotonic solution of sodium chloride before the instillation of 0.5% tetracaine hydrochloride. After topical anesthetization of the rabbit eyes, samples of aqueous humor were obtained by making a limbal puncture with a sterile 26-gauge needle and a sterile tuberculin syringe at intervals of 30, 60, and 120 minutes.

Samples of aqueous humor and vitreous humor were withdrawn 30 minutes, 2 hours, and 6 hours after the subconjunctival injection of terramycin. The eyes were enucleated while the animals were under general anesthesia induced with pentobarbital sodium, injected as "veterinary nembutal® sodium." [5a] These animals were then killed with intravenous injections of air. Four specimens for each time interval were analyzed.

Systemic Administration.—Terramycin hydrochloride in a concentration of 150 mg. per kilogram of body weight was administered to 12 rabbits by the oral route, and 12 rabbits received an intravenous injection of terramycin hydrochloride in a concentration of 50 mg. per kilogram of body weight. These rabbit eyes were enucleated while the animals were under general anesthesia induced with veterinary pentobarbital sodium. Enucleations were performed at 30 minutes, 1 hour, 2 hours, and 6 hours after the systemic administration of terramycin.

TABLE 1.—*Concentration of Terramycin, in Micrograms per Cubic Centimeter, in Aqueous and Vitreous Humor After Subconjunctival Injection of 0.05 Cc. of Solution of Terramycin Hydrochloride (50 Mg. per Cubic Centimeter)*

	Minutes After Administration		
	30	120	360
Aqueous humor	0, 0 0, 0	5, 5 10, 15	0, 0 0, 0
Vitreous humor	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Samples of aqueous humor, vitreous humor, and blood were obtained at the time of enucleation from the rabbits given terramycin orally. The aqueous humor, vitreous humor, blood, cornea, conjunctiva, sclera, iris, chorioretina, lens tendon, muscle, and optic nerve were analyzed for their terramycin content at time intervals of 30 minutes, 2 hours, and 6 hours after the intravenous administration of terramycin. A biologic-cup method of analysis was devised and utilized for these determinations.

RESULTS

Local Administration.—Topical Administration of Drops and Ointments: Topically administered terramycin solution and ointment in the concentrations utilized in these experiments failed to penetrate the normal cornea into the aqueous humor in any detectable amount.

Subconjunctival Injection: Table 1 demonstrates that definite levels of terramycin were found in the two-hour samples of rabbit aqueous humor after the subconjunctival injection of terramycin hydrochloride in a concentration of 50 mg. per cubic centimeter. The level of terramycin in the aqueous was transient. Therefore, when this concentration is administered by the subconjunctival route, injections more frequent than every six hours will be necessary to maintain a level of terramycin in the aqueous humor. Detectable levels of terramycin were not found in the vitreous humor.

5a. "Veterinary nembutal® sodium" contains per cubic centimeter 60 mg. of pentobarbital sodium, 10% alcohol, and 20% propylene glycol in water.

Systemic Administration.—Oral Use: No detectable amounts of terramycin were found in the aqueous or the vitreous humor one, two, four, and six hours after ingestion of the capsule preparation of terramycin hydrochloride powder.

Intravenous Injection: Definite levels of terramycin were found in the cornea, sclera, aqueous, iris, and rectus muscle of the rabbit eye 30 minutes after the intravenous administration of 50 mg. per kilogram of body weight. This concentration must have rapidly decreased, as no detectable amounts were found in these structures in two- and six-hour specimens.

TABLE 2.—*Concentrations of Terramycin, Expressed in Micrograms per Cubic Centimeter, After Intravenous Administration of 50 Mg. per Kilogram of Body Weight*

	Minutes After Administration		
	30	120	360
Aqueous	20, 5, 5, 5	0, 0, 0, 0	0, 0, 0, 0
Vitreous	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0
Cornea	2, 0	0	0
Conjunctiva	5	< 2	< 2
Sclera	2, 4	0	0
Iris	2, 4	0	0
Chorioretina	0, 0	0	0
Lens	0, 0	0	0
Tendon	0, 0	0	0
Muscle	2, 8	0	0
Optic nerve	0, 0	0	0
Serum	100+	100	20

TABLE 3.—*Effect of Terramycin Hydrochloride on Regeneration of Corneal Epithelium After Topical Administration*

	No. of Eyes	No. of Eyes Whose Epithelium Had Regenerated on Indicated Day				
		1	2	3	4	5
Controls *	8	0	1	4	3	0
Terramycin-treated eyes †	8	0	2	4	1	1

* Hourly instillations of a solution containing sodium chloride, 12.5 mg. per cubic centimeter, and sodium borate, 5 mg. per cubic centimeter of distilled water during the day. Petrolatum was applied at night.

† Hourly instillations of a solution containing terramycin hydrochloride, 5 mg. per cubic centimeter; sodium chloride, 12.5 mg. per cubic centimeter, and sodium borate, 5 mg. per cubic centimeter of distilled water during the day. Terramycin ointment, 30 mg. per gram, was applied at night.

The conjunctiva was the only ocular tissue which maintained a level of terramycin over a six-hour period (Table 2).

TOXICITY STUDIES

Regeneration of Corneal Epithelium.—Standard corneal abrasions were produced in each eye of eight rabbits. The left eye served as the control and received a solution containing 12.5 mg. of sodium chloride and 5 mg. sodium borate per cubic centimeter of distilled water. The right eye was treated with a solution of 5 mg. of terramycin hydrochloride, 12.5 mg. of sodium chloride, and 5 mg. of sodium borate, per cubic centimeter of distilled water. These solutions were instilled hourly during the day. At night, terramycin hydrochloride ointment, 30 mg. per gram of base, was applied to the right eye, while the control eyes received local applications of petrolatum U. S. P.

Table 3 demonstrates that there is no significant difference in regeneration of corneal epithelium between the control eyes and the terramycin-treated eyes. Neither the control nor the treated eyes showed any evidence of secondary infection or corneal scarring.

Marr, Wood, and Storck,[6] using white rats, found no inhibition of corneal-epithelium regeneration by terramycin in a concentration of 250 γ per cubic centimeter.

Tolerance of Human Ocular Tissues.—Over 200 human eyes have tolerated the instillation of terramycin hydrochloride in a concentration as great as 25 mg. per cubic centimeter.

Subconjunctival injections of terramycin hydrochloride in a dose of 0.05 cc. of a solution containing as much as 50 mg. per cubic centimeter have been tolerated by human eyes. There is a moderate amount of pain immediately after the injection, but this discomfort disappears in a few minutes. The rabbit eye tolerates well the subconjunctival injection of terramycin hydrochloride in a concentration of 100 mg. per cubic centimeter.

Intraocular Tolerance Studies.—Anterior-Chamber Injection: A solution of pure crystalline terramycin hydrochloride, as well as a solution of terramycin hydrochloride combined with sodium chloride and sodium borate, was injected into the anterior chamber of rabbit eyes in amounts of 0.05 cc., beginning with a concentration of 2.5 mg. per cubic centimeter of terramycin hydrochloride. No deleterious effects were noted. The concentrations of terramycin employed for injection were gradually increased. The minimal concentration that produced a toxic reaction was 25 mg. per cubic centimeter. The toxic effects consisted of transient iritis and edema of the lower portion of the cornea, due to damage of the corneal endothelium.

The buffered terramycin hydrochloride did not show toxic effects until a concentration of 35 mg. per cubic centimeter was reached. When the concentration of terramycin was further increased, the damage to the cornea and iris was severer and more extensive. The corneal structure became soft and distorted, and the iris tissue disorganized.

Intravitreal Injection: Intravitreal injections of 0.05 cc. of various concentrations of the pure crystalline terramycin hydrochloride, and of the terramycin hydrochloride combined with sodium chloride and sodium borate, were made in rabbit eyes. These injections were made in the area of the pars plana, with the needle directed toward the center of the vitreous humor. Similar injections were made with isotonic solution of sodium chloride and a combination of sodium chloride and sodium borate.

Toxic effects were first noted when 0.05 cc. of a concentration of terramycin hydrochloride, 25 mg. per cubic centimeter, was injected into the rabbit vitreous; the lower portion of the retina showed permanent damage. The combination of terramycin hydrochloride with sodium chloride and sodium borate produced toxic effects when the concentration reached 30 mg. per cubic centimeter of terramycin

6. Marr, W. G.; Wood, R., and Storck, M.: Regeneration of Corneal Epithelium, Am. J. Ophth. **34**:609, 1951.

hydrochloride. Increased concentrations of terramycin damaged the vitreous and retinochoroidal structures more extensively.

Temporary retinal detachment, and subsequent choroidal and retinal atrophy around the site of intravitreal injection occurred with both isotonic sodium chloride solution and the combination of sodium chloride and sodium borate.

Table 4 indicates with the aid of the plus (+) sign the degree of toxicity of various concentrations of terramycin. The minus sign indicates no change in appearance from that of the control eyes, which received both isotonic solution of sodium chloride and the combination of sodium chloride and sodium borate.

TABLE 4.—*Tolerance of Aqueous and Vitreous Humor to Intraocular Injection of Terramycin* *

	Combination, in Mg./Cc., of					Toxicity in	
No. of Eyes	Terramycin Hydrochloride, Mg./Cc.	Terramycin Hydrochloride	Sodium Chloride	Sodium Borate	Isotonic (0.9%) Sodium Chloride Solution	Anterior Chamber	Vitreous
2	..	..	35	87	..	—	—
2	..	..	..	..	0.05 cc.	—	—
2	2.5	..	..	..	..	—	—
2	..	2.5	6.25	2.5	..	—	—
2	5	..	..	..	..	—	—
2	..	5	12.5	5	..	—	—
2	15	..	..	..	..	—	—
2	..	15	37.5	15	..	—	—
2	20	..	..	..	..	±	—
2	..	20	50	20	..	—	—
4	25	..	..	..	..	+	+
4	..	25	62.5	25	..	—	—
4	30	..	..	..	..	++	++
4	..	30	75	30	..	—	+
4	35	..	..	..	..	++	++
4	..	35	87.5	35	..	+	++
2	50	..	..	..	..	++++	++++
2	..	50	125	50	..	++++	++++

* Each injection consisted of 0.05 cc.

COMMENT

It is evident from these studies that terramycin topically, subconjunctivally, and orally administered penetrates poorly into the ocular fluids and tissues of the normal rabbit. Even intravenous administration that produced high blood-serum concentrations allowed only low degrees of intraocular penetration.

Douvas, Featherstone, and Braley have reported similar poor penetration after topical and systemic administration. However, they noted increased penetration of topically applied terramycin in the presence of epithelial abrasions. This increase of penetration in the presence of breaks in the corneal-epithelium barrier has been noted for all other antibiotics so tested, i. e., penicillin,[7] streptomycin,[8] bacitracin,[9]

7. Leopold, I. H., and LaMotte, W. O., Jr.: Penetration of Penicillin in Rabbit Eyes with Normal, Inflamed and Abraded Corneas, Arch. Ophth. **33**:43 (Jan.) 1945.

8. Leopold, I. H., and Nichols, A.: Intraocular Penetration of Streptomycin Following Systemic and Local Administration, Arch. Ophth. **35**:33 (Jan.) 1946.

9. Bellows, J. G., and Farmer, C. J.: Use of Bacitracin in Ocular Infections: Tolerance and Permeability in Rabbit Eye, Am. J. Ophth. **31**:1070, 1948.

aureomycin,[10] chloramphenicol,[11] and neomycin.[12] It is likely that terramycin will penetrate more readily into infected ocular tissues than into normal tissues, as has been demonstrated for other antibiotics.[13]

SUMMARY

Topically applied solutions and ointments of terramycin penetrated poorly into the aqueous humor of the normal rabbit eye.

Subconjunctival injections of an aqueous solution of terramycin hydrochloride containing 50 mg. per cubic centimeter of the drug produced detectable levels in the aqueous humor.

A single intravenous injection in rabbits of a solution of terramycin hydrochloride in a concentration of 50 mg. per kilogram of body weight produced detectable, but transient, concentrations of the drug in the aqueous humor, cornea, conjunctiva, sclera, iris, and rectus muscle.

Terramycin did not inhibit regeneration of corneal epithelium in the rabbit eye.

The human eye tolerates topical instillation of a solution containing 25 mg. of terramycin hydrochloride per cubic centimeter and subconjunctival injections of 0.05 cc. of a solution containing 50 mg. per cubic centimeter of terramycin hydrochloride.

Anterior-chamber and intravitreal injections of 0.05 cc. of a solution containing 20 mg. per cubic centimeter of terramycin hydrochloride were tolerated by the rabbit eye.

Dr. Gladys L. Hobby, of Chas. Pfizer & Company, Inc., Brooklyn, supplied the terramycin used in these studies.

10. Bellows, J. G.; Richardson, V. M., and Farmer, C. J.: Aureomycin in Ophthalmology, Am. J. Ophth. **33**:273, 1950.

11. Leopold, I. H.; Nichols, A., and Vogel, A. W.: Penetration of Chloramphenicol into the Eye, Arch. Ophth. **44**:22 (July) 1950.

12. Vogel, A. W.; Nichols, A., and Leopold, I. H.: Ocular Tolerance and Penetration of Locally Applied Neomycin, Am. J. Ophth. **34**:1357, 1951.

13. Leopold and LaMotte.[7] Leopold and Nichols.[8]

Clinical Notes

TECHNIQUE FOR HANDLING THE SUTURES WHEN INSERTING AN ALLEN ORBITAL IMPLANT

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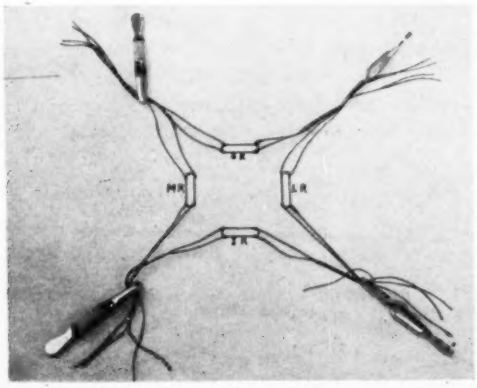
I HAVE used the Allen plastic implant a number of times after enucleation. At first, it was exceedingly difficult to prevent the 16 threads from becoming entangled, and it was especially annoying when one of the clamps on the 4 sutures on one muscle rolled, thus twisting the threads and perhaps the muscle also. In order to obviate these difficulties, I have used the simple plan indicated in the sketch in handling the sutures.



Method of clamping the sutures in order to avoid twisting and entanglement.

This plan consists essentially in placing the sutures from one edge of a muscle in the same clamp with those from the closer edge of the adjacent muscle, and not in the same clamp with the sutures of the other edge. For instance, the suture on the lateral edge of the superior rectus muscle is placed in the same clamp with the sutures from the upper edge of the lateral rectus muscle, whereas the sutures from the medial edge of the superior rectus are placed in the same clamp as those from the upper edge of the medial rectus. Carrying this idea out on all the muscles, one obtains a figure something like that shown in the sketch (Figure).

The advantage of this method lies in the ease with which the sutures are kept straight as they are threaded through the slots in the implant and the ease with which they may be straightened out in the event that a clamp should roll. When a pair of sutures is to be threaded through the slot, it is disengaged from its clamp, placed through the proper slot, and again reengaged in the clamp until all sutures have been threaded into the implant and the muscles are ready to be drawn through the slots. It is, of course, understood that all four sutures from any given muscle must pass through the same proper slot. Sometimes it is of advantage to include a pinch of the drape in the clamp with the sutures.

It has been my practice to attach the sutures to the muscles before separating them from the globe and to place the sutures in the clamps as described above. Then, after all of the sutures are clamped, the muscles are separated from the globe, and the enucleation is completed. After this, the implant is threaded. If desired, it would be possible to thread the implant immediately as the sutures are placed in the muscles, thus eliminating one handling of the sutures, but the difficulty with this, of course, is that the implant is in the way during the enucleation.

The foregoing discussion is not to be interpreted as a recommendation for the use of plastic materials as implants. I have not used enough to form an intelligent opinion. The Allen implants which I have used have all remained in place and have seemed to function reasonably well.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

A CASE OF PHTHISIS BULBI DUE TO CHICKENPOX

THIS CASE is of interest, since most ophthalmic manifestations in cases of chickenpox are referred to as of minor importance.[1] A case of late corneal involvement was reported by Packard, cited by Tassman,[1] Rosenbaum,[2] and Falls and Beall.[3] Conjunctival lesions involving the limbus have been reported by Duke-Elder[4] and Veeneklaas.[5] Duke-Elder[6] mentions a case in which "an acute uveitis resulting in phthisis bulbi was noted by Hutchison (1886-87) in a case of chickenpox—but whether this was incidental or not is difficult to say." In the present case also it is difficult to say whether the development of phthisis bulbi was incidental or not, but the beginning of a severe intraocular inflammation so soon after the onset of chickenpox, the severity of the infection, and its fulminating nature certainly implicate chickenpox in one way or another.

A youth aged 13 broke out with chickenpox on Dec. 26, 1950. There were a low-grade fever and a typical rash on the face and trunk, but not much discomfort. On Dec. 31 the right eye began to itch and then to throb. It became "bloodshot" and had a little stringy mucus in the conjunctival sac. His pediatrician prescribed the use of boric-acid washes and bacitracin ointment locally and administration of chloramphenicol, 250 mg. four times a day, by mouth. On Jan. 2 he was referred to me because the eye showed severe bulbar injection and chemosis. The cornea was diffusely hazy. The anterior chamber was almost filled with "exudate," so the iris was not visible. Centrally, there was slightly less exudate, but no view of the fundus was possible because of haziness of the media in both the anterior chamber and the vitreous. Tension was normal, and corneal sensitivity was present. There was minimal pain but profuse lacrimation. Treatment was continued as prescribed, with the addition of atropine sulfate, 1%, three times a day.

When seen on Jan. 8, the patient presented the same subjective symptoms, but with the feeling of a foreign body under the upper lid. Examination revealed bulging of the cornea and iris in the upper nasal quadrant through a thinned area in the cornea; this descemetocele was 2 to 3 mm. in diameter and rose about 2 mm. above the surface of the cornea. The eye as a whole showed increased reaction, more "exudate" in the anterior chamber, almost filling the whole chamber, and considerable infiltration of the cornea about the descemetocele. Owing to this increased reaction, it was decided not to cover the cornea with a flap.

Two weeks later the descemetocele had receded to the level of the cornea, which by now had noticeably shrunk and had become more generally infiltrated throughout its stroma. There was

1. Tassman, I. S.: The Eye Manifestations of Internal Diseases, Ed. 2, Philadelphia, C. V. Mosby Company, 1942, p. 374.

2. Rosenbaum, H. D.: Am. J. Ophth. **26**:53-56 (Jan.) 1943.

3. Falls, H. F., and Beall, J. F.: Ocular Varicella, Arch. Ophth. **34**:411-412 (Nov.-Dec.) 1945.

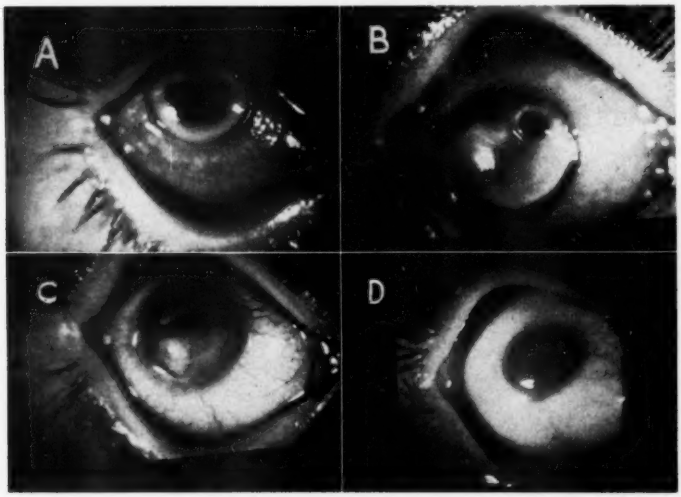
4. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. II, St. Louis, C. V. Mosby Company, 1932, p. 1907.

5. Veeneklaas, G. M. H.: Ophthalmologica **119**:96-98 (Feb.) 1950.

6. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. III, St. Louis, C. V. Mosby Company, 1941, p. 2150.

linear pitting of the surface of the cornea in the lower temporal quadrant, which took the fluorescein stain, showing thinning of the cornea in this area. However, no iris tissue could be seen behind this thinned area or anywhere else, since the anterior chamber was filled with exudate. Pain was absent, and lacrimation was decreasing. There was no light perception at this time.

Two months later the bulbar injection was decreased. The cornea was shrunken and almost totally opaque. Its surface showed a shallow pit at the site of the former descemetocele and a groove in the lower outer quadrant, but no iris or other structures could be seen. There was beginning vascularization at the limbus all around. The globe began to show the typical flattening in the areas of rectus-muscle insertions and bulging of the sclera between these tendon insertions.



Appearance of the eye (*A*) on Jan. 2, (*B*) on Jan. 8, (*C*) on Jan. 26, and (*D*) on March 29, 1951.

This patient was last seen on Jan. 4, 1952. The eye has been quiet for the past nine months. There had been increasing shrinkage of the globe, so that there was some pseudoptosis of the upper lid. The cornea was barely visible and measured 4 mm. in the vertical diameter and 6 mm. in the horizontal diameter. It was almost totally opaque and white and was vascularized lightly over its entire surface. It was the most shrunken globe I have ever seen develop in so young a person in so short a time.

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Ophthalmological Reviews

OCULAR ASPECTS OF MYCOTIC INFECTION

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FUNGI play a complicated role in the world, both aiding and disrupting human welfare.

The dramatic discovery of the curative properties of the substances penicillin,[1] streptomycin,[2] chloramphenicol (chloromycetin®),[3] and others, from refined molds, and the determination of their chemical structure and their synthesis have brought about one of the greatest advances in medicine of all time, and this achievement may be only the beginning of an era in which we are to see new forms of therapy strike crucial blows against diseases as yet uncontrolled.

MYCOSES AND OCULAR DISEASE

This paper is primarily concerned with the whole question of molds as they relate to infection in and about the eye. Such infections are not frequently diagnosed; the average clinician in his lifetime of hospital and office practice may see only one or two proved cases of mycotic infection of the eye. The literature, however, is voluminous and is composed mostly of case reports of infection with individual species of fungi. The clinician, in order to understand his case, must consult authorities in the various related medical specialties and basic sciences.

The ophthalmologist, thinking primarily of ocular infections, is impressed by the number and severity of mycotic infections that have associated systemic lesions and that end with the death of the patient. Priding himself on making systemic, as well as ocular diagnoses, when the occasion warrants, the ophthalmologist must bear in mind the entire subject of mycotic infections, in an attempt to make an early diagnosis in these rare, and sometimes difficult, cases.

There are many forms of fungi which are difficult to connect with any disease process because they are normally present in the eyes, on the skin, in the gastrointestinal tract, and elsewhere. These fungi, as well as the true pathogenic fungi, abound in the soil and air and live as parasites on the vegetation and animals of many parts of the globe. Their virulence varies, but almost all of them require an injury to the host in order to begin their invasion.

1. Fleming, A.: On Antibacterial Action of Cultures of Penicillium, with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**:226-236, 1929; On the Specific Antibacterial Properties of Penicillin and Potassium Tellurite, J. Path & Bact. **35**:831-842, 1932.

2. Riggins, H. M., and Hinshaw, H. C.: Streptomycin and Dihydrostreptomycin in Tuberculosis, Nat. Tuberc. A. Tr., 1949.

3. Smith, R. M.; Joslyn, D. A.; Gruhzit, O. M.; McLean, I. W., Jr.; Penner, M. A., and Ehrlich, J.: Chloromycetin: Biological Studies, J. Bact. **55**:425-448, 1948.

Historical Review.—The recognition of infection of man by molds and fungi goes back to antiquity. Benevenutus Grassus,[4] of Jerusalem, wrote in 1474 A. D. a delightful description of a fungous infection which he described as a fleshy growth generated by a "melancholic humor," between the nose and the eye. He said that it resembled lung substance, and that it was granular and extruded a putrid substance. It had an excessive friability and resembled a gumma. His treatment was adequate for that day; he excised the fungus and, after applying the cautery, dressed the lesion daily with cotton soaked in white of egg.

In tribute to the great medical leaders of the past, upon whose work the foundations of our knowledge rest, one must mention some of the earlier writings and reports of fungous infection. It was in 1839 that Langenbeck [5] first described the fungus causing thrush, and Schoenlein, the fungus causing favus. Much of the early work had to do with general infection and the recognition of various pathogenic fungi. The morphology of some of the major species and the phases of their life cycles were not thoroughly established until about 1880. Some of the prominent names associated with this early research are Gruby (1841),[6] Hering (1884),[7] Rixford and Gilchrist (1896),[8] Castellani (1905),[9] Whitfield (1898),[10] and Jadassohn and Bloch. Sabouraud [11] did much work on the fungi and later published a book focusing attention on the subject. Busse [12] and others too numerous to list here have made notable contributions to our knowledge.[13]

Ocular involvement in many cases was described by early mycologists, including Gilchrist (1896)[14] and Ricketts (1901)[15]. Ricketts' excellent treatise describing "oidiomycosis" (blastomycosis) contains a fine summary of the literature to that date, together with many interesting expositions by his colleagues on the theory of fungous infection in that era. Wilder [16] presented a very complete report of blastomycosis of the eyelid, and Wood [17] also considered this subject exhaustively.

4. Grassus, B.: De Oculis: Eorumque Egritudinibus et Curis, Translated with Notes and Illustrations from First Printed Edition, Ferrara, 1474 A. D., by C. A. Wood, Stanford University, Stanford University Press, 1929, Chap. 39, On the Morus or Fungus.

5. Langenbeck, C. J. M.: Compt. zu Weimar **12**:144, 1839.

6. Gruby, D.: Mémoire sur une végétation qui constitué la vraie teigne, Compt. rend. Acad. sc. **13**:72-75, 1841.

7. Hering, T.: Über Pharynxmycosis leptothricia, Ztschr. klin. Med. **7**:358-371, 1884.

8. Rixford, E., and Gilchrist, T. C.: Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs, Johns Hopkins Hosp. Rep. **1**:209-267, 1896.

9. Castellani, A.: Tropical Forms of Pityriasis Versicolor, Brit. M. J. **2**:1271-1272, 1905.

10. Whitfield, A.: A Case of Mycosis Fungoides, Brit. J. Dermat. **10**:153-158, 1898.

11. Sabouraud, R. J. A.: Les tricophyties humaines, No. 227, Paris, Rueff & Cie, 1894.

12. Busse, O.: Über parasitäre Zelleinschlüsse und ihre Züchtung, Centralbl. Bakt. **16**:175-180, 1894.

13. Further references are listed in the bibliography.

14. Gilchrist, T. C., and Stokes, W. R.: Presence of an Oidium in the Tissues of a Case of Pseudo-Lupus Vulgaris (Preliminary Report), Bull. Johns Hopkins Hosp. **7**:129-133, 1896. Gilchrist, T. C.: A Case of Blastomycetic Dermatitis in Man, ibid. **1**:269-290, 1896.

15. Ricketts, H. T.: Oidiomycosis (Blastomycosis) of the Skin and Its Fungi, J. M. Research **6**:373-546, 1901.

16. Wilder, W. H.: Blastomycosis of the Eyelid, J. A. M. A. **43**:2026-2030 (Dec. 31) 1904.

17. Wood, C. A.: Blastomycosis of the Ocular Structures, Especially of the Eyelids, Ann. Ophth. **13**:92-103, 1904.

Montgomery and Ormsby (1908)[18] reported 27 cases of systemic blastomycosis; in their Cases 1 and 20 the eye was seriously damaged. They emphasized the large number of fatalities that followed systemic invasion.

Ruhrah,[19] of Baltimore (1899), reviewed the occurrence of actinomycosis in America and emphasized the frequently fatal course of the disease. In this article, again, is an excellent list of the early reports on this disease.

Hektoen,[20] of Chicago (1907), summarized and compared the first 13 reported cases of blastomycosis with the first 17 recorded cases of coccidioidal granuloma. This comparison is most interesting in the light of present-day knowledge of coccidioidomycosis.

Research on fungous disease of the eyes was carried on by McKee,[21] Gifford,[22] and Verhoeff,[23] who described both intraocular and extraocular mycotic invasion.

The confusion and difficulty relative to the diagnosis of various ocular mycotic infections are well illustrated by noting the work on leptotrichosis conjunctivae (Parinaud's conjunctivitis). Although Parinaud [24] described the clinical picture in 1899, it was not until 1904 that Verhoeff and Derby [23a] isolated the Leptothrix. Their findings were confirmed by Bernheimer [25] in 1906, and then not again until 1913, when Verhoeff [23b] himself recorded 10 more cases. Lemoine [26] reported another case in 1924, and Gifford [22] discussed the pathogenicity and the various strains of Leptothrix in 1920.

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18. Montgomery, F. H., and Ormsby, O. S.: Systemic Blastomycosis: Its Etiologic, Pathologic and Clinical Features as Established by a Critical Surgery and Summary of 22 Cases, 7 Previously Unpublished; the Relation of Blastomycosis to Coccidioidal Granuloma, Arch. Int. Med. **2**:1-41 (Aug.) 1908.

19. Ruhrah, J.: Actinomycosis in Man, Ann. Surg. **30**:417-451; 605-631; 722-746, 1899.

20. Hektoen, L.: Systemic Blastomycosis and Coccidioidal Granuloma, J. A. M. A. **49**: 1071-1077 (Sept. 28) 1907.

21. McKee, S. H.: Blastomycosis of the Cornea, with a Review of Reported Cases of Blastomycosis of the Eye, Internat. Clin. **3**:50-57, 1926; Tr. Am. Acad. Ophth. **30**:187-197, 1925.

22. Gifford, S. R.: (*a*) Leptothrix on the Conjunctiva and in the Meibomian Glands, J. Infect. Dis. **27**:296-309, 1920; (*b*) Further Note on Ocular Sporotrichosis, Arch. Ophth. **53**:264-266, 1924; (*c*) Diseases of the Eye and Adnexa Due to Fungi and the Higher Bacteria, ibid. **57**:224-237, 1928. (*d*) Gifford, S. R., and Dillon, E. E.: Conjunctivoglandular Syndrome of Parinaud: Report of Case Showing Thread Mold in Sections, Arch. Ophth. **12**:518-524 (Oct.) 1934. (*e*) Gifford, S. R.: Parinaud's Conjunctivitis (Leptothricosis of Conjunctiva), Am. J. Ophth. **10**:484, 1927. (*f*) Gifford, S. R., and Day, A. A.: Leptotrichosis Conjunctivae: Further Report, Arch. Ophth. **31**:423-426 (May) 1944.

23. (*a*) Verhoeff, F. H., and Derby, G. S.: Parinaud's Conjunctivitis, Arch. Ophth. **33**:389-412, 1904. (*b*) Verhoeff, F. H.: Parinaud's Conjunctivitis: A Mycotic Disease Due to a Hitherto Undescribed Filamentous Organism, ibid. **42**:345-351, 1913; (*c*) Mycosis of the Choroid Following Cataract Extraction, and Metastatic Choroiditis of the Other Eye, Producing the Clinical Picture of Sympathetic Uveitis, ibid. **53**:517-530, 1924; (*d*) A Case of Metastatic Intraocular Mycosis, ibid. **55**:225-234, 1926. (*e*) Verhoeff, F. H., and King, M. J.: Leptotrichosis Conjunctivae, Parinaud's Conjunctivitis, ibid. **9**:701 (May) 1933. (*f*) Verhoeff, F. H.: Improved Method of Staining Within Tissues, Leptotriches of Parinaud's Conjunctivitis and Gram-Positive Micro-Organisms, J. A. M. A. **115**:1546-1547 (Nov. 2) 1940.

24. Parinaud, H.: Recueil d'ophthalmologie, 1899.

25. Bernheimer, S.: Ein Beitrag zur Parinauds Konjunktivitis, Klin. Monatsbl. Augenh. **44**:323, 1906.

26. Lemoine, A. N.: Parinaud's Conjunctivitis, with Demonstration of the Leptothrix of Verhoeff, J. A. M. A. **82**:537-538 (Feb. 16) 1924.

As late as 1940 Verhoeff [23f] offered new techniques of staining and isolating the Leptothrix, still a difficult procedure. In the early days leptotrichosis of the conjunctiva frequently persisted six months, whereas now, fortunately, the lesions are usually cured with penicillin in a week or so.

Cogan,[27] commenting on his case of intraocular fungous infection, also indicated the difficulty of making the diagnosis of such an infection. His review of the 11 previously reported cases of endogenous intraocular fungous disease is well worth reading.

FREQUENCY OF MYCOTIC INFECTION

Infection of the human nervous system by fungi [28] occurred in 10 cases encountered among 17,400 autopsies at Johns Hopkins Hospital and in only 4 cases in the Philadelphia General Hospital in the past 20 years.

Candida is thought to be harbored by 10% of the female population at large but occurs in 45% of all pregnant women.[29]

The relation of fungous infection to cancer has recently been stressed, and whether further work will substantiate this assumption will be shown in due time. Kagan [30] pointed out that he found Candida (Oidium) albicans in 93% of 29 cases of cancer of the stomach, whereas mycotic infection of the normal stomach is rare.

During World War II it was believed that at times 90% of the service men had athlete's foot (dermatophytosis), and the prevalence of this disease in the civilian populace is often widespread. As a rule, this condition does not concern the ophthalmologist and often comes to the attention of the physician only because of secondary complications, such as thrombophlebitis or lymphadenopathy.

In my own practice, the frequency of mycotic infections of the eye parallels that of my colleagues, who see but few cases in their lifetime. Dermatophytosis of the eyelids, seen in rare cases, has responded to ammoniated mercury U. S. P. or potassium iodide ointment (7%), and fractional doses of roentgen rays may be used with boric acid soaks and other mild treatment. It is often the secondary infection that causes trouble in the dermatophytoses. Leptothricosis conjunctivae formerly was seen several times a year, but since the advent of antibiotics it is rarely encountered and easily cured. Obstructions of the nasolacrimal duct with mycotic plugs present themselves perhaps once or twice a year. The only case of possible systemic mycotic disease in my files was one in which the diagnosis was incomplete and in which a fungus was not proved to be the etiologic factor; the case was one of pulmonary infection in which both corneas sloughed off during the acute phase of the illness.

It is my impression that the diagnosis of many fungous infections is missed either because the condition clears up before the physician has cause to run a series of cultures, or because many laboratories are not equipped to deal with fungous infections and only the more chronic lesions are sent for diagnosis to specially trained persons.

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27. Cogan, D. G.: Endogenous Intraocular Fungous Infection: Report of a Case, Arch. Ophth. **42**:666-682 (Nov.) 1949.

28. Stratemeier, W. P.: Mucormycosis of the Central Nervous System: Report of a Case, Arch. Neurol. & Psychiat. **63**:179-180 (Jan.) 1950.

29. Campbell, N. S., and Parrott, M. H.: Vulvovaginal Moniliasis, Am. J. Obst. & Gynec. **59**:1005-1012, 1950.

30. Kagan, J. R.: Correspondence, New England J. Med. **242**:159, 1950.

Dermatologists have been most prominent in the development of our knowledge of mycology, because of the frequent cutaneous manifestations in the mycotic invasions of the body. Modern dermatologists do not make the diagnosis of fungous disease as often as they used to in 1930 and 1940. Formerly, all recalcitrant eruptions of the hands and feet were diagnosed as fungoid. Recently, owing to improved laboratory procedures, this diagnosis has been reduced by 50 or 75%. In an analysis of 200 cases (Andrews,[31] 1949) of recurrent pustular infection of the hands, it was impossible to find any cause in 36% of the cases. Fungi were deemed pathogenic in 27%; contact dermatitis was the cause in 8%; bacterial invaders were responsible in 5%; allergy was the cause in another 5%, and foci of infection elsewhere in 19%. Sixty-four per cent of the patients had had their eruptions over one year, while 11 had had them 10 years and 2 all their lives. One-third of the patients were housewives, and most of the rest were physicians and dentists.

CLASSIFICATION OF FUNGI

Ophthalmologists need not be concerned with a detailed classification [32] of molds and fungi, but they should appreciate the differences and a few of the properties that separate molds and fungi from true bacteria, filtrable viruses, Rickettsia, and Protozoa.

Fungi are a large group of plant-like micro-organisms that grow in filaments, or "hyphae," and intertwine in a mat-like growth, called the mycelium. Spores, or the reproductive bodies, may contain one or more cells; they arise from the colony, or mycelium. This mat-like growth constitutes an undifferentiated plant, without leaves, stems, or roots. Plants of this rudimentary type are classified as Phylum Thallophyta. Fungi do not contain chlorophyll and are unable to synthesize carbohydrates from the carbon dioxide of the air; consequently, they are either saprophytic or parasitic. Algae also belong in this phylum, but are separated from fungi because they contain chlorophyll.

Pathogenic fungi are found chiefly among two groups of the Thallophyta:

1. Schizomycetes
   - A. Actinomyces (halfway between bacteria and higher molds)
   - B. Nocardia
2. Fungi imperfecti (lacking sexual spores)
   - A. Dermatophytes (invade skin, hair, and nails)
     - (*a*) Microsporums
     - (*b*) Trichophyton
     - (*c*) Epidermophyton
   - B. Cryptococcus neoformans (C. hominis; C. meningitidis)
   - C. Candida albicans (thrush, vulvovaginitis, moniliasis)
   - D. Blastomyces dermatitidis (Gilchrist [14] and Stokes 1896)
   - E. Blastomyces brasiliensis (pseudococcidioidal granuloma; granulomatous form of coccidioidomycosis)
   - F. Histoplasma capsulatum (disease of reticuloendothelial system like kala-azar)
   - G. Sporotrichum schenckii (subacute chronic granulomatous infection of the skin, lymph nodes and subcutaneous tissue)
   - H. Coccidioides immitis (coccidioidomycosis)
   - I. Monosporium apiospermum
     - (*a*) Madura foot
     - (*b*) Actinomyces mycetoma
   - J. Hormodendrum pedrosoi (chromoblastomycosis)

31. Andrews, G. C.: Possible Prevention of Cancer in Chronic Radiodermatitis by Medical Means, Connecticut M. J. **13**:105-108, 1949.

32. International Rules for Botanical Nomenclature, adopted by Fifth International Botanical Congress of Cambridge, 1930, ed. 3, compiled by John Briquet, June, 1935.

DIFFERENTIAL DIAGNOSIS OF MYCOTIC INFECTION

Mycotic diseases are of such common occurrence that experts[33] in this field consider them in the differential diagnosis of practically every obscure infection. One of the handicaps that restricts the early diagnosis of mycotic disease is the comparatively small number of laboratories equipped to carry out specific identification of fungi. Few ophthalmologists are equipped to carry on the study of their cases by more than direct microscopic examination of material obtained locally. They must rely on trained technicians for culture, animal inoculation, and other specific means of recognizing fungi. Owing to cultural and morphologic variations in the growth of all fungi, considerable experience is required to make specific differentiations of various species.

A brief description of some of the diagnostic steps that may be taken by the ophthalmologist, and some of the procedures he may request in the laboratory, will be of interest.

Fungi are identified macroscopically by their characteristic type of colony formation and the fusion of their mycelium, and microscopically by the type of spores. For instance, a colony of Actinomyces bovis will grow in the bottom of a broth-culture tube as a small white growth, easily broken up by shaking, and will be Gram-positive, while the various species of Nocardia will appear on the surface of Sabouraud's dextrose agar slants, will be irregularly folded and will vary in color from cream to deep orange, or even red. Nocardia asteroides will be acid-fast, while Nocardia madurae is not acid-fast.

It is impractical in this paper to discuss in detail the cultural characteristics of all the pathogenic fungi and the various types of spore formation. Extreme caution should be exercised in handling pathogenic fungous cultures, because in many cases the spores or the mycelium is highly infectious. Several fatalities have occurred among laboratory workers.

Fungous cultures go through various stages, and some cultures may require one month before the growth can be ascertained to be nonpathogenic (Histoplasma capsulatum). At certain stages in their growth they may be mistaken for other fungi. The H. capsulatum, for instance, greatly resembles Blastomyces dermatitidis at one stage of culture.

Histologic Study.—Most of the pathogenic fungi produce a tubercle-like giant cell granuloma. Pathogenic fungi all form hyphae, or irregularly segmented filaments, in the human body, but spores are rarely recognized, except in artificial culture.

Pus, conjunctival smears, sputum, spinal fluid, pleural fluid, blood, feces, and gastric contents—all are to be examined directly when indicated. Specimens of these materials may be examined unstained, in subdued light, or they may be cleared in a drop of 10% potassium hydroxide. Sometimes a drop of India ink will reveal the capsules of the Cryptococcus. Gram's stain and the Ziehl-Neelsen stain for acid-fast organisms are often valuable, with many others. Search is made for the granules of Actinomyces, for budding cells, filaments, capsules and spherules, or sporangia, with endospores.

33. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. S.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1949.

Often, direct examination gives negative results, and other studies must be made, both to identify and to determine the pathogenicity of the possible invaders.

Fungous Cultures.—Suitable media for culture of suspected fungoid material may be blood, beef or veal infusion, broth, or dextrose agar. Sabouraud's dextrose agar slants are excellent for many types of colonies. Transplantation for several generations of growth, and differential growth on other media such as corn meal agar or the various sugars, are required for the identification of many species. Some of the fungi grow rapidly, and others require several weeks of growth and study for their identification. Filtered ultraviolet radiation may be used to assist in the study of Tinea capitis and Tinea versicolor. Some fungi have still to be cultured.

Bacterial contaminants are not alone in confusing the cultural problems of fungi. Species of Penicillium, Aspergillus, Mucor, and many other molds that abound in the air of all places may be found so frequently in some cultures that they appear to be the pathogenic factor. Mycologists are reluctant to ascribe any pathogenicity to these common contaminants, although in some cases they agree that they may act as secondary invaders.

Immunization Reactions.—The local and generalized reactions seen with the use of penicillin, derived from the mold Penicillium, as well as with other antibiotics, leaves little doubt as to the manifold expression of sensitization in the body. All molds and fungi have immunologic functions, when they invade as pathogens or when they are used in therapy.

Storm van Leeuwen [34] showed that 50% of his asthmatic patients were sensitive to mold allergens. Brown [35] showed that asthma is often due to molds, even the saprophytic species. In investigating sensitization to fungi, the ophthalmologist must keep in mind even the so-called benign species of fungi. This is even more logical when the size of the spores (3 to 5μ) is compared with the size of the common air-borne pollen grains (15 to 40μ).

Some of the better-known reactions to fungi (or their products) are (1) contact dermatitis; (2) syndrome-like serum sickness, often with shock and angioneurotic edema; (3) sensitization of other organs, such as the bronchial tubes (asthma) and kidney; (4) toxic reactions, such as agranulocytosis, neuritis, and convulsions; (5) indirect reactions, such as precipitation of unrelated infections by destruction of antagonistic bacteria or production of infection by penicillin-resistant bacteria.

Cutaneous immunization reactions may be used as a method of establishing a diagnosis in certain fungous infections. These are not infallible, and a knowledge of tests is required before one should rely on them for diagnosis. One of the most widely used is the trichophytin test for ringworm. This test is considered valuable when the response is positive, and also when it is negative, since a nonreacting person is thought to be free of that particular mycotic infection.

There is considerable evidence to prove that the specificity of the cutaneous reaction to coccidioidin, blastomycin, and sporotrichin is of positive diagnostic value. Blastomycin, however, is known in some instances to give a negative

34. Storm van Leeuwen, W.: Bronchial Asthma in Relation to Climate, Proc. Roy. Soc. Med. (Sect. Therap. & Pharm.) **17**:19-26, 1924.

35. Brown, G. T.: Sensitization to Fungi, Ann. Int. Med. **6**:655-671, 1932; Hypersensitiveness to Fungi, J. Allergy **7**:455-470, 1936.

cutaneous reaction in the presence of active disease, and so is histoplasmin. Ability to detect cross sensitization and false-positive reactions can hardly be ascribed as essential to ophthalmologists.

Animal Inoculation.—Animal inoculation of mice or rats for suspected cases of blastomycosis, coccidioidomycosis, cryptococcosis, or sporotrichosis may bring about more rapid diagnosis than can be obtained from cultures. Of the genus Candida, only C. albicans is pathogenic for laboratory animals. Rabbits given intravenous injections die in four or five days. The Histoplasma produce visceral lesions in guinea pigs or mice after intraperitoneal injection. In some cases the lesions present in man cannot be reproduced in laboratory animals.

Agglutination Tests.—These tests, although not always to be relied upon, are available for moniliasis and North American blastomycosis and coccidioidomycosis.

Roentgenography.—This method is of great value in cases of pulmonary invasion by the Aspergillus, Geotrichum, Blastomyces, Coccidioides, and Actinomyces. It may be of value in other fungous diseases. Many workers are inclined to believe that some of the calcified pulmonary plaques formerly considered tuberculous are really mycotic.

TYPES OF MYCOTIC INFECTIONS OF THE EYE

The majority of pathogenic fungi produce superficial lesions of the skin and about the eyes in addition to systemic lesions, while only a few types are limited in their scope to the superficial involvement of the skin, eyes, and their adnexa.

The only truly superficial mycotic invaders, which do not produce systemic infection, are the ringworm infections, and possibly some of the tropical fungi. Rhinosporidium may be included in this group, although it has not been cultured and positively identified as a fungus.

The lacrimal apparatus, the eyelids, and the conjunctiva often yield a fungous growth on culture. True saprophytic fungi, as well as pathogenic types, may be cultured from these exposed parts. The history of trauma is often encountered in cases of ocular lesions when the fungi are the etiologic agent.

Fazakas [36] found over 42 species of fungi by culture of material from various diseases of the eyelids, conjunctiva, and lacrimal apparatus. Many fungi were secondary invaders in cases of gonorrheal conjunctivitis, vernal conjunctivitis, herpetic keratitis, and hordeolum. In other cases, such as those of chronic corneal ulcer, chronic croupous conjunctivitis, eczematous keratoconjunctivitis, and infections of the lacrimal sac, various molds have been considered the etiologic agent. In cases of mild blepharitis and conjunctivitis, in which cultures are usually not obtained, it is difficult to say how often a fungus is the etiologic factor.

In mycotic infections of the eye, it is important to think of the fungi as belonging to three categories: (1) the saprophytic fungi, or contaminants; (2) the superficial invaders; (3) the dangerous fungi that produce both superficial lesions and deep, granulomatous lesions or blood dyscrasias. Fungous infection may also reach the eye by metastasis from distant organs, as well as through sensitization phenomena.

36. Fazakas, S.: Role of Fungi in Evolution of Eye Diseases, Orvosi hetil. **81**:723-724, 1937; Über die Schimmelpilze des gesunden und kranken Auges, von Graefes Arch. Ophth. **138**:416-423, 1938; Pilzbefunde in den Tränenkanälchen, an den Augenlidern und den Lidrändern, Klin. Monatsbl. Augenh. **104**:59-63, 1940.

SUPERFICIAL MYCOTIC INVADERS ABOUT THE EYE

Among superficial mycotic invaders, producing ringworm infections (dermatomycoses), are Tinea pedis, Tinea manuum, T. capitis, Tinea barbae, Tinea glabrosa, Tinea cruris, and T. versicolor. Erythrasma, trichomycosis, piedra, and otomycosis are also to be classified under superficial mycotic infections.

Dermatologists, who are most concerned with the dermatophytoses,[37] believe that this type of mycotic infection is a reaction to the invasion of the body rather than a true infection. DeLamater and Benham [38] believe that differences in the virulence of individual strains of fungi are more important than differences in the species.

Ringworm Infections.—Ringworm may involve the eyelids and face adjacent to the lids, especially in children (T. capitis). It often occurs in epidemics and may by carried by pets, especially strays. Overcrowding and lack of hygienic facilities predispose to this type of infection. The cornea and conjunctiva are rarely involved.

Bedell [39] reported a case of corneal ulcer, the result of an injury from a cow's tail, from which he had isolated the Cephalosporium (related to Trichophyton gypseum). Treatment with potassium iodide was successful.

Numerous bizarre types of lesions of the skin are seen, and the differential diagnosis is primarily the task of the dermatologist, who must demonstrate a focus of pathogenic fungi.

Rhinosporidiosis of the Conjunctiva.—This disease, recently brought up to date by Edmunds and Beck (1948),[40] has been reported in less than 200 cases. Barnshaw and Read [41] reported a case in Philadelphia in 1939 and reviewed the literature to that date. Many cases have been reported from India (Wright [42] 1922; Duggan,[43] 1928, and Rao, 1931) and 18 cases have been reported from North America.[33]

Rhinosporidiosis is a localized fungous infection of the mucous membranes, usually nasal or conjunctival, although the penis may be involved. It is often transmitted from animals. Males seem to be chiefly infected, although four cases were reported in the female in India. It has also been reported in conjunction with leprosy. The nasal lesion is a single large vascular polyp with minute white granules on the surface (sporangia).

Ocular lesions may appear silently on the conjunctiva, resembling the granulation tissue remaining after spontaneous drainage from a chalazion. Often they are subject to removal several times before microscopic examination discloses the sporidial invader.

37. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

38. DeLamater, E. D., and Benham, R. W.: Experimental Studies with Dermatophytes: Primary Disease in Laboratory Animals, J. Invest. Dermat. **1**:451-467, 1938; Experimental Studies with Dermatophytes: Immunity and Hypersensitivity, Produced in Laboratory Animals, ibid. **1**:469-488, 1938.

39. Bedell, A. J.: Cephalosporium Keratitis, Tr. Am. Ophth. Soc. **44**:80-84, 1946.

40. Edmunds, M., and Beck, R.: Rhinosporidiosis of Conjunctiva: Case Report, Virginia M. Month. **75**:278-280, 1948.

41. Barnshaw, H. D., and Read, W. T., Jr.: Rhinosporidiosis of the Conjunctiva, Arch. Ophth. **24**:357-361 (Aug.) 1940.

42. Wright, R. E.: Rhinosporidium Kinealyi of the Conjunctiva, Indian M. Gaz. **57**:81-82; 82-83, 1922.

43. Duggan, J. N.: Case of Rhinosporidium Kinealyi, Brit. J. Ophth. **12**:526-530, 1928.

Culture is difficult, and animal inoculation is often unsuccessful. The organism in rhinosporiosis may be a sporozoon or a phycomycete.

LEPTOTHRICOSIS (TRICHOMYCOSIS AXILLARIS)

Leptothricosis is generally a silent, often tropical, disorder in which nodes develop on the axillary hair. Culture is extremely difficult, and special media are required, as for A. bovis.

Leptothricosis Conjunctivae.—This form was defined by Verhoeff [23a] in 1904 and described as a form of Parinaud's conjunctivitis, a uniocular conjunctivitis with extensive preauricular lymphadenitis. This ocular infection bears no relation, so far as is known, to leptothricosis axillaris. Verhoeff [23e] reported 45 cases in the vicinity of Boston up to 1933. The finding of the Leptothrix in the conjunctiva has been confirmed (Lemoine,[26] 1924; Gifford,[22e] 1927; Gifford and Dillon,[22d] 1934, and Harner,[44] 1934). Culture or identification by Verhoeff's Gram stain is difficult.

Treatment of leptothricosis conjunctivae is by excision of the gray areas in the conjunctiva, with biopsy, and use of penicillin parenterally shortens the duration of the lymphadenitis.

Leptothrix was found by Gifford [22a] in simple conjunctivitis which did not resemble the Parinaud type. The organism may be a common inhabitant of the conjunctival sac, and often only a mild pathogen.

Bartels [45] isolated the Leptothrix from stained teeth in 1943.

Gifford and Dillon [22d] remarked on the difficulty of isolating and staining the Leptothrix of Verhoeff and suggested the use of other tests in order to rule out tularemia, tuberculosis, and actinomycosis. The diagnosis can then be made by exclusion, dependent, of course, on staining by Verhoeff's method and culture by the techniques of Verhoeff and King.[23e] Gifford and Day [22f] stated the belief that properly stained material offers a greater likelihood of indicating the diagnosis than the use of cultures.

OCULAR ASPECTS OF INFECTION BY MOLDS THAT PRODUCE SYSTEMIC DISEASE

All mycotic infections may have their initial lesion in the external portion of the eye and its appendages. The ophthalmologist must be fully aware of the importance of the systemic involvement that may follow, or cause, ocular mycotic infection, with the majority of the fungi pathogenic.

Most of the molds infect the external portion of the eye. If operation is performed without proper cleansing of the conjunctival sac, intraocular infection with fungi may follow operation. The use of mild protein silver U. S. P. and copious irrigation eliminate any molds in the conjunctival sac. The use of penicillin as an irrigant during operation may prevent many intraocular infections.

The following 11 groups of mycoses that have proved syndromes of both ocular and systemic importance will be considered: (1) Moniliasis (Candida albicans), (2) actinomycosis, (3) mycetoma, (4) nocardiosis, (5) sporotrichosis, (6) blastomycosis, (7) histoplasmosis, (8) coccidioidal mycosis, (9) granuloma paracoccidioides, (10) cryptococcosis (torulosis), and (11) aspergillosis.

44. Harner, C. E.: Parinaud's Coniunctivitis, Am. J. Ophth. **17**:629-639, 1934.

45. Bartels, H. A.: Filamentous Micro-Organism Isolated from Stained Teeth, J. Dent. Res. **22**:97-102, 1943.

Moniliasis

C. albicans is a yeast-like organism which produces numerous unrelated manifestations on the skin, eyelids, and cornea (Sykes [46] 1946) and in the lungs. This fungus is isolated so frequently from the skin, stools, and vagina that the diagnosis of a resulting pathologic condition is often difficult. It is often a secondary invader and should be considered as the etiologic agent in serious infection only if other causes are excluded and the patient shows hypersensitivity to the fungus.

C. albicans is never found on normal skin, although it often inhabits the gastrointestinal tract. The incidence of moniliasis increases with age, and relapse often occurs in the presence of debilitating illness, especially diabetes. The common sites of initial infection are the intertriginous spaces, and extensions over large areas of skin are common. Vaginitis, as well as thrush, is caused by the Candida. The systemic form often resembles tuberculosis, and the organism has even been obtained from the heart valves.[47] Moniliasis may also occur as an acute respiratory infection, such as pneumonia. This disease should be considered a serious infection, especially in diabetic patients. It may end fatally.

Ocular Complications in Moniliasis.—Keratomycosis (moniliasis) is rarely seen in the cold climates and usually follows some sort of trauma to the eye produced by an earthy substance. The mycotic corneal ulcer is usually shallow and indolent, with undermined and infiltrated edges. The floor is usually covered with a thin, dry membrane, firmly adherent to the corneal tissue.

Iritis and hypopyon often occur in the active stage. Perforation of the globe is rare. Near the limbus the lesion may resemble fascicular keratitis. Ulcerative keratomycosis is caused by other molds (Aspergillus and Streptothrix) more frequently than by Candida. Culture in any case of suspected keratitis is therefore important. Candida can be seen and cultured easily.

Mycotic keratitis may take varied forms. Sykes [46] reported a case, verified by culture, in which the disease appeared identical with dendritic keratitis. These lesions improve with large doses of iodides.

Obstruction of the nasolacrimal duct is frequently reported to be due to C. albicans. The case described by Fine and Waring,[48] of San Francisco, is typical.

A woman of 25 had epiphora of 24 hours' duration. Irrigation of the obstructed duct yielded a cast of the nasolacrimal duct, 16 by 3 mm., which resembled soft dough in color and consistency. Cure resulted. The eyes were normal. The cast was composed of budding yeast cells and a few cocci and diphtheroids. Culture showed C. albicans.

Treatment of C. Albicans Infection.—General measures are important, including supplementary vitamins, diet and rest when the infection is systemic. Vaccine therapy is of doubtful value. Ascending doses of iodides are helpful. X-rays are useful in the treatment of accessible areas which will not be damaged by the

46. Sykes, E. M.: Fungous Infection of the Cornea: Case Report of Keratomycosis Due to Monilia, Texas J. Med. **42**:330-332, 1946.

47. Geiger, A. J.; Wenner, H. A.; Axilrod, H. D., and Durlacher, S. H.: Mycotic Endocarditis and Meningitis: Report of Case Due to Monilia Albicans, Yale J. Biol. & Med. **18**:259-268, 1946.

48. Fine, M., and Waring, W. S.: Mycotic Obstruction of Nasolacrimal Duct (Candida Albicans), Arch. Ophth. **38**:39-42 (July) 1947.

rays. Local dermatologic remedies are useful. Cody [48a] reported two cases of moniliasis of the vocal cords successfully treated with streptomycin. All foci of infection with C. albicans, especially in the gastrointestinal tract, should be eradicated. Systemic infection is often fatal.

Actinomycosis Streptothricosis

Actinomycosis.—The actinomycete is a bacteria-like anaerobe. This group of organisms branch like the molds, but are small, like the Eubacteriales. They are slender, measuring 1 μ in size. They reproduce like bacteria and produce spores in their filaments.

Actinomycosis is most widely distributed throughout the world. It may be localized superficially, and be cured by vigorous treatment, or it may become generalized and cause the death of the host.

Chloramphenicol (chloromycetin®), a new antibiotic, obtained from the cultures of Streptomyces venezuelae, has recently been found useful in the treatment of bacterial, rickettsial, and viral infections.

Actinomyces bovis (Streptothrix actinomyces) has caused most of the infections. More than half the persons affected are from agricultural regions. A. bovis may normally be isolated from the mouth, tonsils, and gastrointestinal tract of healthy persons. It was present in 47% of the tonsillar crypts of 100 tonsillectomy patients (Emmons).[49] When inoculated into animals, only 50% became infected. The characteristics which make A. bovis a pathogen are not understood. This explains why there are such various reports in the literature, the lesions ranging from simple conjunctivitis to destruction of the skull and meningitis with death.

Actinomycosis (streptothricosis) conjunctivae commonly causes concretion in the canaliculi.

On the conjunctiva, the fungus produces nodular granulations (1 mm. or less in diameter), which may be pedunculated and may occur on the bulbar conjunctiva. In the acute cases larger yellow follicles have been described, associated with lymphadenopathy.

Abscesses of the conjunctiva, as well as membranous conjunctivitis, are described. Histologically, such acute lesions show epithelioid cells and cells with polymorphous nuclei with giant cell reactions (Wilson 1930).

Dacryocystitis, as well as corneal ulcers of varying severity, have been described as due to actinomycosis. Bruce and Locatcher-Khorazo,[50] reported the recovery of the Streptothrix in a case of superficial punctate keratitis. Snyder reported a resistant form of ophthalmia neonatorum due to the Streptothrix. An actinomycete has been recorded as invading the orbit and eye from the sinuses and from the jaw after dental extraction. In these cases death occurred. Verhoeff [28] reported a case of actinomycosis following cataract extraction which produced metastatic

48a. Cody, C. C., Jr.: Moniliasis of Larynx: Report of 2 Cases, Ann. Otol. Rhin. & Laryng. **57**:371-376, 1948.

49. Emmons, C. W.: Strains of Actinomycosis Isolated from the Tonsils, Puerto Rico J. Pub. Health **11**:72, 1936; Pub. Health Rep. **53**:1967, 1938; Medical Mycology, Bot. Rev. **6**:474-514, 1940.

50. Bruce, G. M., and Locatcher-Khorazo, D.: Actinomyces: Recovery of the Streptothrix in Case of Superficial Punctuate Keratitis, Arch. Ophth. **27**:294-298 (Feb.) 1942.

choroiditis of the other eye and a clinical picture of sympathetic disease. He also reported a metastatic lesion in an enucleated eye, which was followed by the death of the patient from endocarditis.

Actinomycotic endocarditis was considered and two cases were reported by Wedding,[51] who also feels that fungous diseases offer a challenge in diagnosis that is not met as frequently as could be.

Fuchs [52] also reported actinomycosis in enucleated eyes after cataract extraction.

Thorson and Mueller [53] described a case of unilateral exophthalmos due to actinomycosis, which persisted for 5 years before a cure.

Harley and Wedding [54] reported a case of uveitis, meningoencephalitis, and alopecia due to Actinomyces.

When the disease develops, often after trauma, the initial lesion is usually about the head. In 50% of the cases the infection begins in the head, often on a membranous surface, and often about the eye.

The differential diagnosis includes all the granulomatous diseases, including sporotrichosis, coccidioidomycosis, and tuberculosis. Cultures of sputum which yield actinomycetes are often misleading because the fungus is frequently saprophytic in the mouth. The lesions simulate syphilis, carcinoma, and pyoderma, and there may be an elevated sedimentation rate and leucocytosis.

The diagnosis depends on finding the ray fungus in the pus and on culture.

Treatment of actinomycotic infections is by early excision, when possible, and administration of large doses of iodides. Occasionally, intensive x-ray therapy will be of value. The sulfonamides are sometimes effective. Thymol in 1:1,000 aqueous solution is said to destroy the actinomycotic parasite in 45 seconds and may be tried on local lesions. Penicillin is often beneficial.[55] McVay and associates [56] reported aureomycin to be curative. Torrens and Wood [57] reported streptomycin to be valuable.

Nocardiosis (actinomycosis without granules).—This type of actinomycosis is due to a common saprophyte of the soil and causes systemic lesions similar to those of A. bovis. The organism has been isolated from deep lesions in glands and vital organs, including the brain. It is an aerobic fungus. With other fungi, it may invade the eye.

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51. Wedding, E. S.: Actinomycotic Endocarditis: Report of 2 Cases with Review of Literature, Arch. Int. Med. **79**:203-227 (Feb.) 1947.

52. Fuchs, E.: Ein Fall intraokulärer Aktinomykose, von Graefes Arch. Ophth. **101**:14, 20, 24-31, 111, 991, 1920.

53. Thorson, J. A., and Mueller, E. F.: Probable Actinomycosis of Orbit, J. Iowa M. Soc. **31**:70-72, 1941.

54. Harley, R. D., and Wedding, E. S.: Syndrome of Uveitis Meningo-Encephalitis, Alopecia, Poliosis and Dysacousia: Report of Case Due to Actinomyces, Am. J. Ophth. **29**:524-535, 1946.

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Benedict and Iverson [58] described a case of chronic keratoconjunctivitis which had existed for 16 years and in which they proved the etiologic agent to be Nocardia. No form of treatment was of benefit, including local use of penicillin, 1,000 units per cubic centimeter, every hour for two weeks. Eight cultures, made over four years, yielded the Nocardia. Other organisms were present, but were believed to be secondary.

Mycetoma (actinomycosis; maduromycosis).—This disease begins with a subcutaneous swelling. It may appear on the eyelids (Aldridge and Kirk [59]). Two cases involving the eyelids are known since 1920. The histologic picture is typical of a granulomatous lesion. In India the common type of lesion involves the foot, and an injury is usually necessary to start the infection. Reilly and Steel [60] (1949) reviewed the recent literature and noted that many cases have been found in the United States, over one-half being from Arizona, Texas, and California.

Many fungi are described as causing the disease, but the pathogenicity and specificity of all these have not been settled.

The clinical course of the disease in India, from the appearance of the subcutaneous swelling, which ruptures to form sinus tracts and progresses slowly for as long as 30 years, until the foot is greatly enlarged (four to five times normal), requiring amputation, is not fully understood. The wearing of shoes is a sufficient preventive.

In the differential diagnosis syphilis, tuberculosis, yaws and other fungous diseases, elephantiasis, and malignant neoplasms must be excluded. The treatment is surgical, since no known medical agents bring about improvement.

Sporotrichosis

Numerous species of Sporotrichum are common saprophytes in all parts of the world, and many human and animal carriers have been found. The greatest number of cases have been found in South Africa, France, and the Mississippi Valley. Ten cases of ocular involvement have been reported in the United States.[61] The epidemiology of the disease is not clear, because animal, and even human, inoculation (of volunteers in South Africa by du Toit [62]) did not reproduce the disease. Infection is probably due to contact with infected vegetation at the site of a local injury.

De Beurmann and Gougerot [63] defined six types of human lesions, some of which did not appear for three months after the inoculation.

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Ocular involvement (de Beurmann and Gougerot [63a]) is reported as severe conjunctivitis, followed by parenchymatous keratitis (Amias [64]) or panophthalmitis, with metastases to the joints and subcutaneous tissues and death. Metastasis is rare.

Wilder and McCullough [65] reviewed 16 cases of ocular involvement and reported a case. They concluded that trauma is not required for mycotic invasion of the eye and pointed out the systemic symptoms that may arise from ocular involvement.

Gordon [61] reviewed 47 cases and added 1 of his own, in which the lesions appeared to involve the upper lid. He believed that iodides are specific therapy for sporotrichosis.

The upper and lower eyelids are frequently involved by a granulomatous, spreading lesion. Lymphangitis does not always develop. In untreated patients deeper organs are affected, and death is reported frequently.

Sporotrichotic conjunctivitis was reported in 58 cases by Hamburger [66] (1912), in which the typical nodules broke down to form indurated ulcers. Toulant [67] reported 23 cases of ocular involvement, with the following distribution: primary ocular lesions, 13 cases, in 4 of which the disease was fatal; metastatic intraocular lesions from generalized sporotrichosis, 6 cases; involvement of the lids, 6 cases; conjunctivitis, 6 cases; the tear sac, 1 case; the brow, 1 case; the orbit, 3 cases. No essential change in distribution was reported by Gordon [61] (1947).

Gifford [22] reported two cases of involvement of the ethmoid bones following dacryocystitis due to the Sporotrichum. This organism is suspected of being a frequent invader and should often be considered in cases of blepharitis.

The common type of lesion is a sporotrichotic chancre, which must be differentiated from other mycoses, syphilis, tuberculosis, tularemia, and pyoderma. Other types of sporotrichosis, both disseminated and localized, are described. Lesions appear successively along a lymphatic chain.

Diagnosis is possible only by culture. In this method of diagnosis the organism is found to grow well at room temperature on ordinary media. After two weeks a typical mycelium may be studied. S. schenckii is one of the more pleomorphic fungi.

Treatment is mainly with ascending doses of iodides. X-ray therapy may assist in the blocking of lymphatic channels. Penicillin and sulfonamide drugs are of no avail. Surgery is contraindicated.

Blastomycosis (Gilchrist's Disease)

Blastomyces is a widely found yeast of importance in bread making and alcoholic fermentation. Infection by B. dermatitidis is considered a North American disease, except in a case reported by Brody [68] and proved by culture.

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The first lesion is a papulopustule, usually on the skin of the face or hands. The tongue or lungs may be first involved. There is gradual enlargement until an elevated plaque is formed, with some crusting and seropurulent secretion.

Ocular blastomycotic infection frequently involves the lids, according to Wood [17] (9 of 35 cases). McKee [69] cited Pusey,[70] who reported nine cases, with involvement of the lids in six; he expressed the belief that probably in 25% of cases at least the infection has a predilection for the lids. The disease progresses rapidly, with periods of quiet, until it has spread over the entire face and to distant areas if not recognized early. There is frequent distortion, with ectropion and scarring. According to some authors, the conjunctiva is usually immune to the infection, which is said to spread directly from the eyelids to the cornea, producing corneal ulcer. The rare conjunctival involvement takes the form of a rapidly growing granuloma, which may form a ring about the cornea (Ferguson, 1938). Schwartz [71] reported the first case of metastatic infection of the eye from generalized blastomycosis. Other cases have been reported to follow perforation of blastomycotic corneal ulcers and to occur after operation. Cassady [72] discussed uveal blastomycosis and reported a case.

In differential diagnosis, it is necessary to demonstrate the causative organism. Pus from the edge of small abscesses should be examined. Double-contoured budding cells may be observed. Animals may be used to differentiate blastomycosis and infection with C. immitis. The guinea pig dies of coccidioidosis but is not affected by blastomycosis. Reactions to vaccine may help, as well as complement fixation. Other granulomatous lesions which must be ruled out are tuberculosis, bromoderma, epithelioma, sarcoid, and other fungous lesions.

Treatment, when begun before systemic involvement, is usually successful. After that the disease is 90% fatal (Jacobson [73]). Surgical intervention when the lesion is small and cutaneous is the easiest way in which to eradicate the disease. X-irradiation and use of iodides offer the best therapeutic results. Desensitization is advocated by Martin and Smith [74]; antiserum may also be helpful. Supportive measures are very important. Martin and Smith [74] asserted that the treatment of the systemic infections are unsatisfactory. The mortality is much higher than in tuberculosis.

Cryptococcosis (European Blastomycosis; Torulosis)

The Cryptococcus, a yeast, has a predilection for the central nervous system. The onset of the disease may be with dimness of vision, or blindness, and headache, and often comes on after upper respiratory tract disease. Paralysis and convulsions may occur. Stiffness of the neck, neuroretinitis, choked disks, diplopia, and strabismus may all be found, with or without fever.

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Blair,[75] in reviewing the 60 cases in the literature up to 1943, found that in 50% the disease was confined to the central nervous system, in 15% lesions were of the lungs only, and in 13% the disease was generalized.

Cohen [76] emphasized the importance of the association of cryptococcosis and Hodgkin's disease, a relation not previously mentioned in the ophthalmic literature, he stated, and occurring in 10% of the cases of cryptococcosis. He emphasized the importance of early smears and cultures of spinal fluid in cases of suspected cryptococcosis.

The causative micro-organism is Cryptococcus neoformans (C. hominis or Torula histolytica), and is commonly found in the gastrointestinal tract and on the skin.

Diagnosis is possible by culture of spinal fluid on dextrose agar. Thick-walled budding cells are found in centrifuged specimens of the spinal fluid, and occasionally of the blood or sputum.

Weiss and associates [77] (1948) described the only known case of intraocular cryptococcosis. The first eye showed a "cystic growth" in the retina and was enucleated. Three months later the same process destroyed the sight in the second eye. Trephine of the sclera yielded a brownish fluid, from which was cultured the C. neoformans. A second culture was made a few weeks later and showed the same organism. The patient died in 1946; autopsy was not performed.

In the differential diagnosis tuberculosis, meningitis, encephalitis, syphilis, brain tumor, and abscesses are to be excluded. The outcome is usually fatal.

Jesse [78] reported a recent cure in the first case of cryptococcosis of bone (hip) in the literature. The disease responded to surgery and use of penicillin and sulfadiazine. Treatment by penicillin, sulfonamides, and large doses of iodides is valuable if the diagnosis is made before an advanced stage.

Granuloma Paracoccidioides

Granuloma paracoccidioides (Blastomycosis Brasiliensis; South American Blastomycosis) may often resemble coccidioidosis and blastomycosis, although involvement of the intestine does not occur in true coccidioidal infection or blastomycosis and does occur in the paracoccidioidal variety. Lesions are granulomatous and often occur around the face. Lymphadenopathy may occur, to simulate Hodgkin's disease. Most frequently the mouth is involved, rather than the eyes. Differential diagnosis includes exclusion of the usual infectious diseases.

Aspergillosis

Aspergillus is a very large group of easily isolated fungi. Aspergillus fumigatus is probably one of the few pathogenic varieties. The lungs are most frequently, and often primarily, involved.

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A. fumigatus may produce an intractable and chronic ulcer of the cornea and has been reported as causing perforation of the cornea, together with loss of the globe (Castroviejo and Munoz Urra [79]). Vitreous infection has been found; it was thought to be endogenous (Huber, Lorenz [80] and Stock [81]). In the latter cases the eye was lost.

Rychener [82] reported a case of intraocular aspergillosis following a penetrating injury; he reported 18 other cases of intraocular mycotic infection of various types. He emphasized that with more careful study the diagnosis would be made oftener.

Donahue [83] (1949) reported an infection with Aspergillus niger in a 12-year-old girl, discoloring the lower punctum and conjunctiva and involving the lacrimal sac. Identification of the organism was easy. A cast of the lacrimal region was believed to have been formed, and irrigation resulted in cure.

Lesions about the skin of the head and the mucous membranes of the eye and nasopharynx are reported. The bones and meninges have been invaded. Blepharitis and dacryocystitis were also reported by Rosenvold [84] (1942).

The treatment is usually supportive, together with large doses of iodides.

Cawley [85] reviewed the literature and reported a case in which the infection was present from birth and the child lived 7½ years before dying of the infection.

Coccidioidal Mycosis

C. immitis has been isolated from the soil, the vegetation, and many of the cattle in the San Joaquin Valley, of California, where it is endemic. The general manifestations of the disease are widespread and unpredictable and may occur in epidemics.[86] Patients may show nothing more than a mild respiratory infection, or they may succumb within a few weeks. The lungs, bones, joints, and blood stream may be involved.

Ocular involvement in coccidioidomycosis has been reported as resembling phlyctenular conjunctivitis (Smith [87]), and conjunctivitis is said to have occurred in 4 of 100 cases (Willett and Weiss [88]). Levitt [89] (1948) reported a case of retinitis

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of proliferative type, with subsidence in 30 days, in a case of active coccidioidomycosis of the lung.

Davis [90] reported that 13 cases of cerebral coccidioidal mycosis have been listed in the Army Institute of Pathology. He reported an additional case. No cutaneous lesions were present, and roentgenograms of the skull and chest revealed nothing abnormal. Examination of the eyes revealed bilateral papilledema, and sixth nerve paresis developed in the seventh week of illness. Until necropsy the diagnosis was considered to be tuberculous or syphilitic meningitis.

Smith, Beard, and Saito [91] made the diagnosis by recovery of the fungus in 40% of cases, by positive serologic reactions in 49%, and by a positive response to the coccidioidin test and a negative response to the tuberculin test in 11% of 274 cases.

Evaluation of treatment is handicapped by frequent periods of spontaneous remission. In general, therapy should be supportive and symptomatic.

Recent studies show that chloramphenicol may be of value in treating coccidioidmycosis.[92]

Histoplasmosis

This rare, and usually fatal, disease is caused by H. capsulatum. The infection is disseminated via the reticuloendothelial system, like lymphosarcoma. Blood smears may show the intracellular parasite. Cultures often take a month before a proper diagnosis can be made. The eye is not often involved, although the primary feature which would suggest this disease is lymphadenopathy. All sorts of lesions of the mucous membrane of the eyes, nasopharynx, and mouth are reported. It is suggested that there is a widespread nonfatal type of infection in various parts of the world which is not recognized.

Kunstadter, Whitcomb, and Milzer [93] reported what they believed to be the first case of proved benign histoplasmosis, which they followed from onset to cure.

Meleney [94] reviewed 32 cases and discussed 13 more; he believes that the disease will be recognized more readily in the future. While the fungus has not been found free in nature its portal of entry is the skin or the respiratory or gastrointestinal tract. Infection may be through a biting insect, as well as from an animal harboring the fungus.

Treatment depends on early diagnosis. Meleney believes the best results are obtained with organic antimony salts, such as stibophen U. S. P. (fuadin®) or stibarmine glucoside.

Until knowledge of this disease is more widespread, ophthalmologists must suspect it in cases of lymphadenopathy, skin ulcers, or undiagnosed anemia and asthenia with an evening rise of temperature, or of chronic pulmonary infections.

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Martz [95] reported the case of a child in which, among others, the diagnosis of chloroma, or leukemic infiltration, was considered, until the Histoplasma was seen in necropsy sections.

Mider, Smith, and Bray [96] reported a case in which both H. capsulatum and C. neoformans were considered the specific etiologic agents. This impression was confirmed at autopsy.

A fine public health survey [97] of histoplasmosis was performed in Loudoun County, Va., without uncovering any evidence of mild infection.

Recent studies show that the antihistaminic drugs inhibit the growth of H. capsulatum when the organism is incubated on horse serum and that they may offer another means of therapy (Carson and Campbell [98]).

The fact that only 71 cases of histoplasmosis were reported between 1906 and 1945, whereas 42 additional cases were reported between 1945 and 1949 [99] shows that more efficient recognition of some of the mycotic diseases is now possible. Some experts [100] believe that histoplasmosis is the cause of sarcoidosis, and others, that it is the etiologic factor in lymphoblastoma.

SUMMARY

Consideration of the ocular aspects of mycotic infection is inseparable from a consideration of fungous infection in general. This is in accord with the view of ophthalmologists who pride themselves on making the diagnosis of systemic, as well as ocular, disease when the occasion warrants.

Two types of ocular mycotic infection are recognized: (*a*) infection by molds which produce superficial lesions only, and (*b*) infection by molds which produce both deep systemic and ocular lesions.

Diagnosis and treatment of fungous infection of the eyes, especially with the systemic invaders, present a major problem to ophthalmologists, as well as to others of the medical profession.

The literature abounds in case reports depicting the protean manifestations of fungous infections of the human body. New types are being reported, and old syndromes are being refocused in the light of present-day knowledge. Diseases rarely recognized are now being diagnosed with increasing frequency. Diseases heretofore restricted to certain endemic areas are showing up in new localities. The ophthalmologist who has had isolated experiences with mycotic lesions in the past should consider the subject as a whole, so that he may allot to each type of fungous infection its proper place.

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From the hundreds of species of fungi that may be found in and about the eye, either primarily or by metastasis, 14 pathogenic groups deserve detailed attention at this time.

As with other rare diseases, the diagnosis is not possible unless the possibility of the infection is kept in mind.

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Annual Reviews

DISEASES OF THE UVEAL TRACT

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THIS SURVEY of the literature extends from October, 1950 to October, 1951. Several articles are included which were omitted from the previous annual review.

EXPERIMENTAL INVESTIGATIONS

Sondermann [1] differentiates two types of pigment in the human eye: (*a*) an epithelial pigment, which has its origin in the nucleus of the retinal pigment cells, and (*b*) mesodermal pigment, which is dopa-positive. The mesodermal pigment arises from the nuclei of erythroblasts. At the stage of the primary and secondary optic vesicles the developing eye is surrounded by a large number of capillaries, which later become obliterated. They contain erythroblasts, and during the stage of obliteration the nuclei of the erythroblasts give rise to the mesodermal pigment. The degree of mesodermal pigmentation depends upon the time of obliteration of the embryonal vessels and disappearance of the erythroblasts. In heavily pigmented animals the capillaries and erythroblasts persist for a longer period in intrauterine life than in poorly pigmented animals.

INFLAMMATIONS

General Considerations.—The term "collagen diseases" has been introduced in recent years to include a group of conditions which were previously regarded as separate and distinct entities. The basis of this classification is the fact that the alteration of the affected tissues is comparable and that similar tissues are involved in each disease. In addition, the changes which occur in the tissues are dependent in each instance upon a so-called hypersensitivity reaction. It has been suggested by some authors that these diseases are not primarily disturbances of collagenous tissue but that they involve the entire mesenchymal defense unit. This unit is composed principally of cells forming the reticuloendothelial system, the basic unit of which is the reticulum cell. In the presence of a proper stimulus reticulum cells furnish histiocytes, monocytes, and granulocytes. They also form antibodies, the immune globulins, which are associated with the formation of lymphocytes and plasma cells. Substances which provoke activity on the part of the defense unit cause the formation of antibodies in the tissues, as well as an accumulation of globulin antibody from the reticuloendothelial system. The constitution of the patient and his hormonal reactions affect the response to a stimulating factor. Histologically, early sensitivity reactions provoke changes which are distinct and

From the Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine.

1. Sondermann, R.: Pigment Development in the Eye, von Graefes Arch. Ophth. **150**:580-591, 1950; Biological Significance of Mesenchymal Pigment in the Eye, Ophthalmologica **122**:166-171 (Sept.) 1951.

are entitled fibrinoid degeneration. After the development of necrosis the lesion loses its identity. If the walls of the capillaries are affected, the permeability is increased. The reticulum responds by proliferation, and in the early stages macrophages, plasma cells, and lymphocytes are observed. In the later stages, when necrosis occurs, neutrophiles and eosinophiles appear. A group of diseases such as polyarteritis nodosa, rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, scleroderma, temporal arteritis, and serum sickness have been included in this category. The agent which produces these diseases is unknown. The reaction occurring in serum sickness is probably due to a sensitivity to proteins. In some of these conditions the provoking agent is a chemical, a hypersensitivity to the products of hemolytic streptococci, or a hormonal disturbance. The ocular manifestations of the diffuse collagen diseases have been presented in two articles.[2] Polyarteritis nodosa may affect the choroid and produce visible ophthalmoscopic lesions, which appear as circumscribed edematous areas accompanied with diffuse uveitis; iridocyclitis has been noted. According to Hollenhorst and Henderson, 26 of 35 patients with polyarteritis nodosa exhibited abnormal ocular changes. In a number of examinations of eyes obtained at necropsy lesions have been found in the choroidal and ciliary arteries. The ocular lesions of rheumatoid arthritis are well known and primarily affect the anterior uveal tract. It has been observed frequently that in rheumatoid uveitis the posterior uvea is rarely affected. The reason for this selective distribution of the uveal lesions is unknown.

A considerable number of interesting and stimulating articles dealing with inflammation of the eye have been reported during the past year. Many of these concern the etiology of uveal inflammations; others deal with the effects of treatment. Most of the therapeutic results have already been presented in a previous annual review by Leopold.[3] Some are recounted to improve the detail with reference to a particular disease.

Experimental Studies.—Von Sallmann, Locke, and Locke[4] investigated the cytologic and bacteriologic changes in the aqueous humor in cases of uveitis. An attempt was made to verify the observations of Amsler, Verrey, and co-workers. The authors emphasized the difficulty encountered in differentiating cells in aspirated aqueous after degenerative changes have commenced and the cells are separated from their natural matrix. They found that the microphage was responsible for most of the phagocytosis which occurs in experimental infections of the anterior chamber. The cells of the iris participate moderately, and normal endothelium participates not at all. Cytologic studies of centrifuged cells in samples of aqueous humor from the eyes of patients with uveitis did not provide information which would establish the etiologic diagnosis in these cases. The aqueous humor was examined in 88 patients with uveitis of various types. The cells failed to exhibit bacterial phagocytosis except in one instance of postoperative inflammation. Micro-

2. Hollenhorst, R. W., and Henderson, J. W.: Ocular Manifestations of the Diffuse Collagen Diseases, Am. J. M. Sc. **221**:211-222 (Feb.) 1951. Stillerman, M. L.: Ocular Manifestations of Diffuse Collagen Disease, A. M. A. Arch. Ophth. **45**:239-250 (March) 1951.

3. Leopold, I. H.: Annual Review: Pharmacology and Toxicology, A. M. A. Arch. Ophth. **45**:159-224 (Aug.) 1951.

4. von Sallmann, L.; Locke, J. C., and Locke, B. D.: Cytological and Bacteriological Studies of the Aqueous Humor in Uveitis, A. M. A. Arch. Ophth. **46**:4-13 (July) 1951.

organisms were obtained on culture of the aqueous humor in only three cases of endogenous uveitis. In two of the three cases contamination could not be excluded with certainty.

Bick and Wood [5] pointed out that heparin modifies anaphylactic reactions and may inhibit the typical Arthus phenomenon in rabbits sensitized to horse serum. In previous studies they have shown that heparin enters the intraocular fluids only after the capillary permeability had been disturbed, and that if heparin is placed in the eye its presence can be detected for approximately 24 hours. They have also shown that heparin administered to hypersensitive rabbits prior to the injection of antigen protects the animals against uveitis. In the present study they endeavored to explain the effects of heparin if it is administered simultaneously with the antigen or after the antigen has entered the eye. The experiments were carried out on albino rabbits which were sensitized to horse serum, as measured by the anti-horse-serum precipitin titer. The rabbits were divided into groups having similar precipitin titers. It was found that severe uveitis was produced in sensitized rabbits by the introduction of antigen into the anterior chamber; when the heparin was introduced into the eyes at the same time as the antigen, the uveitis was greatly inhibited. If heparin was given systemically after antigen had been introduced into the eye, the uveitis was markedly inhibited.

Mueller [6] discussed the pathogenesis of nonpurulent uveitis and the role of allergy in endogenous nonpurulent uveitis. A series of 861 cases of uveitis which had been observed during the past 10 years were reviewed from the clinic in Heidelberg. The disease was due to an infectious allergy in 50% of the cases. In 25% the uveitis was of tuberculous origin, and in 5% it was due to syphilis. Uveitis is of tuberculous origin if the patient shows active tuberculosis which has passed the stage of a primary infection. By the time the uveitis is active, however, the tuberculosis usually is inactive in the lung. The frequency of various sites of uveitis is discussed, and the ratio of anterior uveitis to posterior uveitis to panuveitis is 5:2:1. Tuberculous uveitis usually involves the posterior portion, while infectious allergies most commonly affect the anterior uvea. Three hundred ninety-five males were affected, as compared with 466 females.

Tuberculous Uveitis.—Onfray and Onfray [7] discuss two cases of atypical tuberculosis. The first patient, a woman, had uveitis and a strongly positive Mantoux reaction. She was treated in the usual manner for one year, without result. She was then given a methylic antigen (a purified tuberculin) which caused a severe focal reaction in the eye, requiring enucleation. The second patient had bilateral sclerosing keratitis and iritis. One eye was eventually enucleated. The histologic picture was one of tuberculosis, but tubercle bacilli were not found. The authors stress the polymorphism of the tubercle bacillus, which explains the variety of clinical forms which are observed in this disease. Perić-Sajvert [8] reports a patient having four

5. Bick, M. W., and Wood, R. M.: Heparin and Uveitis, Am. J. Ophth. **33**:1878-1881 (Dec.) 1950.

6. Mueller, H.: Pathogenesis of Nonpurulent Uveitis and the Role of Allergy in Nonpurulent Uveitis of Endogenous Origin, von Graefes Arch. Ophth. **150**:423-458, 1950.

7. Onfray, R., and Onfray, M.: Uveal Tuberculosis and Atypical Tuberculosis, Bull. Soc. franç. opht. **63**:233-247, 1950.

8. Perić-Sajvert, F.: Tuberculosis of the Choroid with Retinal Detachment, Med. Arkh. **3**:49-58, 1950.

tubercles in the choroid of the left eye, followed by retinal detachment, all of which came on as a focal reaction to systemic tuberculin therapy. After two-months' treatment the retinal detachment subsided, and the choroidal lesions were observed as circumscribed areas of atrophy. Engel [9] cites experiences with a purified tuberculin ("G. T.") and the leucocyte response in patients suspected of having ocular tuberculosis. When tuberculosis is suspected, he tests the patient wih the purified tuberculin and watches the behavior of the leucocyte count. If the blood picture changes after a dose of 1 tuberculin unit of this purified tuberculin, he considers that the diagnosis of tuberculosis is certain. He believes that purified tuberculin is therapeutically superior to ordinary old tuberculin. Frandsen [10] reports the occurrence of unilateral posterior uveitis in three youths, 15 to 18 years of age, after vaccination with Calmette's (purified) tuberculin. The uveitis occurred 2, 3, and 18 months, respectively, after the vaccination. The clinical course of the disease in these patients was of the usual type in tuberculous uveitis. Linhart [11] reviews the effects and complications of BCG vaccination, stating that one of the unfavorable effects is the danger of contaminating or mixing strains of tubercle bacilli. Occasionally draining nodules and fistulae may occur at the site of vaccination. Regional lymphadenopathy occurs in 2.5% of patients so vaccinated. The author reports the case of a 20-year-old student nurse who was vaccinated with BCG in February, 1949; five weeks later severe bilateral iridocyclitis developed, with three hemorrhagic chorioretinal lesions near the macula of the right eye. The uveitis persisted for a considerable period and was complicated by the development of bilateral optic neuritis. At the same time, there developed ulcerative colitis with intermittent fever. Eventually, after six months, the eyes became quiet; vision was 20/20 in the right eye and was limited to light perception in the left eye. Elefteriou [12] reports the case of an infant who died of tuberculous meningitis. A tuberculoma was observed in the choroid. Histologically, the tuberculoma was composed of masses of epithelioid cells and giant cells surrounded by leucocytes and young connective tissue cells. Rohrschneider,[13] in a discussion on ocular diseases associated with chronic active tuberculosis of other organs, states that in an earlier publication he found a 10% incidence of ocular tuberculous disease. He cites other authors, who found from 14 to 45% of ocular involvement in patients with tuberculosis of other organs. In most instances chorioretinal lesions were observed in the periphery of the fundus; these lesions were small and caused no subjective symptoms. To determine the specificity of the peripheral chorioretinal lesions in the fundus of tuberculous patients, he examined 207 persons with pulmonary tuberculosis and 200 persons without active tuberculosis. Seventeen per cent of the tuberculous patients showed peripheral fundus lesions, and 16% of the nontuberculous patients showed lesions

9. Engel, H. J.: Experiences with "Purified Tuberculin" and the Leucocyte Count in Affections of the Eye Suspected to be of Tuberculous Nature, Klin. Monatsbl. Augenh. **117**:476-495, 1950.

10. Frandsen, E.: Eye Lesions After Calmette Vaccination, Acta ophth. **28**:499-510, 1950.

11. Linhart, W. O.: Induced Ocular Tuberculosis, A. M. A. Arch. Ophth. **46**:271-276 (Sept.) 1951.

12. Elefteriou, D., and Joannides, T.: Tuberculoma of the Choroid in a Case of Tuberculous Meningitis, Bull. Soc. hellen. opht. **17**:250, 1950.

13. Rohrschneider, W.: Ocular Diseases in Chronic Active Tuberculosis of Other Organs, von Graefes Arch. Ophth. **150**:592-599, 1950.

of the fundus. This incidence seemed to prove that healed circumscribed chorioretinitis occurs with equal frequency in patients with active tuberculosis and in those without tuberculosis.

Treatment: Parisi [14] reports 14 cases of ocular tuberculosis in which treatment was with streptomycin. In eight cases the iris and ciliary body were affected; in 4, the choroid; in 1, the sclera, and in 1, the cornea. In 12 cases streptomycin was given intramuscularly. Streptomycin ointment was applied topically in one case, and in the last case dihydrostreptomycin and paraaminosalicylic acid were given. The patients received from 41 to 385 gm. of streptomycin intramuscularly over periods of from 39 to 187 days. The daily dose varied from 1 to 2 gm. The average patient received approximately 60 gm. over a period of two months. Ten of the patients had active tuberculosis elsewhere in the body. Of the 14 patients, 10 showed improvement. In four of the patients the ocular disease was considered of tuberculous origin, and two of these four showed improvement. Five of seven patients with probable tuberculous uveitis showed improvement. For the remainder the diagnosis was presumptive, and all were benefited by treatment. Toxic reactions occurred in only four patients. Lepri [15] points out the possibilities of antibiotic therapy in ocular tuberculosis and indicated that equal hope of success cannot be held in all the pathologic conditions produced by the tubercle bacillus, especially some of the paratuberculous forms. The author reports the case of a woman aged 60 who had tuberculous arthritis of the knee joint and pleuropulmonary residua. For several years she had had chronic iritis of the left eye, which had led to almost complete occlusion and seclusion of the pupil. Pronounced congestion developed, and examination showed a large hemispherical nodule on the anterior surface of the iris. The reaction to the tuberculin test was negative. The patient was treated with 0.5 gm. of streptomycin twice a day, 2 gm. of paraaminosalicylic acid every four hours, and thiosemicarbazone (0.1 gm. a day). On the day after therapy was instituted, a large conjunctival nodule appeared; it was excised and showed the histologic picture of tuberculosis. Streptomycin was later given subconjunctivally twice a day (0.1 gm. dissolved in 0.5 ml. of saline solution and 0.2 ml. of 1% epinephrine hydrochloride). A rapid regression of swelling and infiltration of the conjunctiva occurred. At the same time the iris nodule subsided, and one month later all symptoms had disappeared. The author recommends that streptomycin be given in cases of tuberculosis in a dose of 1 gm. daily and that paraaminosalicylic acid be given in a dose of 12 to 15 gm.

Woods and co-workers [16] describe the effect of paraaminosalicylic acid and of streptomycin and paraaminosalicylic acid in normal rabbits with experimental ocular tuberculosis. The anterior chamber of the right eye of 64 rabbits was inoculated with 0.1 cc. of a six-week culture of a virulent human strain of Mycobacterium tuberculosis, diluted so as to contain approximately five organisms to each oil-immersion field. Three weeks later the animals were divided into four groups:

14. Parisi, P. J.: Ocular Tuberculosis Treated with Streptomycin: A Report of 14 Cases, Am. J. Ophth. **34**:393-401 (March) 1951.

15. Lepri, G.: Chemo-Antibiotic Therapy of Ocular Tuberculosis, Am. J. Ophth. **34**:871-874 (June) 1951.

16. Woods, A. C.; Wood, R. M., and Naquin, H. A.: Studies in Experimental Ocular Tuberculosis: XV. Effect of Paraaminosalicylic Acid and of Streptomycin plus Paraaminosalicylic Acid in Normal Rabbits, A. M. A. Arch. Ophth. **45**:546-554 (May) 1951.

Group 1 served as an untreated control; Group 2 was given paraaminosalicylic acid; Group 3 was given paraaminosalicylic acid and streptomycin, and Group 4 was treated with thiazolsulfone (promizole®) and streptomycin. Treatment was continued for 88 days, and all four groups were observed for an additional 104 days. At the end of the experiment all the rabbits were killed and the eyes removed for further study. The group receiving streptomycin and thiazolsulfone and the group receiving streptomycin and paraaminosalicylic acid showed less tuberculous activity than the group receiving paraaminosalicylic acid alone. At the completion of treatment the eyes of all rabbits receiving streptomycin and thiazolsulfone were free of active inflammation, and the eyes of all but one of the group receiving streptomycin and paraaminosalicylic were likewise free of activity. In the 104-day period of observation after termination of treatment there were no recurrences in any of the group receiving streptomycin and thiazolsulfone. Two recurrences occurred in the group receiving streptomycin and paraaminosalicylic acid, and five other animals showed minimal or questionable activity at the time they were killed. In the group receiving paraaminosalicylic acid alone there were no definite recurrences. Horne and Macaskill [17] found that subconjunctival administration of paraaminosalicylic acid resulted in a very high concentration within the aqueous humor within 30 minutes; a therapeutic level was maintained for three hours. Intramuscular injection of paraaminosalicylic acid resulted in concentrations in the aqueous humor which were generally lower than those obtained in the blood. Intramuscular injection, however, maintained a therapeutic concentration in the aqueous for probably less than 90 minutes. The authors determined the effect of paraaminosalicylic acid alone and paraaminosalicylic acid given in conjunction with streptomycin on experimental tuberculous infection of the iris and ciliary body in nonimmune rabbits. All treated groups fared better than the controls. In the dose used by the authors paraaminosalicylic acid appeared to have little beneficial effect, and no significant enhancement of the effect of streptomycin was observed. In the group treated with paraaminosalicylic acid the disseminated lesions of the lungs were severer and showed more numerous tubercle bacilli than did the lesions in the other treated groups and in the controls.

Sarcoidosis.—Lewis [18] reviews 23 cases of generalized sarcoidosis; in 6 ocular changes were exhibited. In five cases bilateral iridocyclitis was present, and in one there was keratitis. In only one case were nodules noted in the iris. In two cases secondary glaucoma developed, and in four, corneal involvement. The visual end-results in many cases were good. In cases requiring operation for secondary glaucoma the eyes reacted well to surgical treatment. In no instance was there progression to destruction of the eye. That the prognosis in the ocular lesions of sarcoidosis is not always good is attested to by an additional case report,[19] in which the patient had sarcoidosis, parotitis (left side), and paralysis of the left side of the face. Bilateral iridocyclitis developed about six months after onset of the parotitis and persisted for approximately one year. Vision was reduced to light perception

17. Horne, N. W., and Macaskill, J.: Effect of Para-Aminosalicylic Acid (PAS) Alone and in Association with Streptomycin in Experimental Ocular Tuberculosis, Brit. J. Ophth. **35**:459-466 (Aug.) 1951.

18. Lewis, N.: Ocular Manifestations of Sarcoidosis with a Description of 7 Cases, M. J. Australia **2**:582-585 (Oct.) 1950.

19. Pearlman, M. D.: Uveoparotid Fever: Heerfordt's Disease, Am. J. Ophth. **34**:299-300 (Feb.) 1951.

in each eye because of severe corneal scarring and vascularization. A skin biopsy showed the usual features of sarcoidosis. Friedman [20] reports a case in which there were bilateral iridocyclitis and the general manifestations of sarcoidosis. The patient was unable to tolerate treatment with calciferol because of a toxic reaction. During the course of the disease haziness of the corneas developed, due to white, dust-like opacities. Acute glaucoma occurred in the right eye; a basal iridectomy was performed, without complication. The author suggests the possibility that calciferol may have caused the corneal infiltrates, and he cites a previous article by Meesmann, who described similar corneal opacities in a patient receiving calciferol (vitamin D_2).

Ocular Leprosy.—Only one article of importance on ocular leprosy has appeared during the past year.[21] The author reports the findings in 55 cases of leprosy, in 34 of which ocular complications were exhibited. It was found that the ocular disease varies directly with the duration and severity of the leprous cutaneous changes. The author found penicillin of no value in the treatment of the ocular lesions; he indicates that riboflavin helped in some cases in which superficial punctate keratitis was exhibited. He reports the observation of yellow sclera in four cases, in all of which the condition was followed by plastic iritis. Yellowing of the sclera in ocular leprosy has not previously been reported, and, according to the author, it is to be considered a serious omen in this disease.

Sympathetic Ophthalmia.—An unusual case of sympathetic ophthalmia is reported [22] in which a farmer, aged 57, was injured in the right eye, with the development of sympathetic ophthalmia. Four months later the left eye exhibited signs of papillitis and posterior uveitis, which eventually resolved almost completely, vision being restored to 6/5 within three months. The patient was apparently completely well until 2½ years later, when acute iridocyclitis again occurred in the remaining eye. The inflammation was severe and persistent and eventually led to secondary glaucoma with atrophy of the eyeball. The authors could not be certain whether the iridocyclitis which developed 2½ years after the initial attack was due to sympathetic ophthalmia; however, the progress of the disease suggested sympathetic ophthalmia. In questioning the patient, it was found that he had had intermittent attacks of watering and photophobia during the 2½-year period. The authors cite a case reported by Verhoeff in which the patient had eight relapses during a period of eight years. Scheffler [23] reported a case in which severe purulent endophthalmitis developed after cataract extraction, followed by atrophy of the eye. The eye was enucleated and showed all the signs of sympathetic ophthalmia. Two and one-half months after the operation iridocyclitis developed in the fellow eye. The author indicates that sympathetic ophthalmia may develop in eyes which are subject to purulent endophthalmitis, as has previously been shown by Samuels. The aqueous [24] of patients with sympathetic ophthalmia sometimes shows numerous eosinophiles. The author stated that if hypertension develops during the course of

20. Friedman, H. S.: Boeck's Sarcoid: A Review and a Report on a Case Demonstrating Multiple Iris Nodules, Acute Secondary Glaucoma, and Keratopathy, Am. J. Ophth. **34**:1126-1136 (Aug.) 1951.

21. Gilchrist, J. S.: Eye Complications of Leprosy, M. J. Australia **1**:8-11 (Jan. 7) 1950.

22. Sichel, A. W., and Louw, J. G.: Sympathetic Ophthalmitis of Unusual Onset, Brit. J. Ophth. **34**:695-697 (Nov.) 1950.

23. Scheffler, M. M.: Sympathetic Ophthalmia, Am. J. Ophth. **34**:1427-1430 (Oct.) 1951.

24. Desvignes, P.: Problem of Sympathetic Ophthalmia, Arch. opht **11**:61, 1951.

sympathetic uveitis the prognosis is grave. He had tried to produce experimental sympathetic ophthalmia by injecting the virus of herpes simplex between the ciliary body and the sclera of rabbits, but the results were inconstant. Witmer and Moser [25] point out that an intercurrent disease, especially one associated with fever, has a beneficial effect on inflammations of the eye. They cite the case of a 7-year-old boy with typical sympathetic ophthalmia. An exacerbation developed two months after enucleation of the exciting eye. Treatment had no effect. An attack of measles with fever caused the eye to become quiet within five weeks. Laws and Howard [26] report a case of sympathetic ophthalmia which occurred 19 days after the injury to the exciting eye. The exciting eye was enucleated, and the patient was given a total of 500 mg. of corticotropin during a period of eight days. The uveitis subsided rapidly, and the patient was followed for almost a year, without a sign of recurrence; vision was 20/20. Previous treatment with antibiotics had been ineffective in this case.

Ocular Brucellosis.—Woods [27] emphasizes that there is nothing characteristic in either the clinical or the histologic picture of ocular brucellosis. He notes that certain types of nummular corneal infiltrates suggest brucellosis. Likewise, low-grade recurrent iritis with gradually forming granulomatous changes and slow spread of the disease through the uveal tract, followed by phthisis bulbi, is the usual picture of brucellar uveitis. Spink,[28] in a discussion on human brucellosis, indicates that 80% of the cases occur in rural people and in employees in the meat-packing industry. He points out that the disease cannot be diagnosed exactly on the basis of the history or the symptoms and that laboratory procedures are most useful in the diagnosis. The agglutination test is the most reliable laboratory procedure for the screening of suspected cases. Cultural studies on the blood are extremely difficult to carry out. He states that the most encouraging therapeutic results are obtained with the use of aureomycin, streptomycin, or sulfadiazine. He suggests that the paucity of reports of ocular brucellosis in patients with acute and chronic brucellosis is due to the fact that the lesions have not been searched for by competent observers.

Toxoplasmosis.—Ruchman and Fowler [29] studied the localization and persistence of Toxoplasma in the tissues of experimentally infected white rats. Organisms were shown to be present in the blood four hours after intraperitoneal injection; they were present daily thereafter for the following week. The maximal concentration was reached between the fourth and the fifth day, and organisms were found sporadically in the blood during the next several weeks. Parasites were found in small numbers in the liver, spleen, and lungs four hours after inoculation. They were then found more regularly for 7 days in the liver, 9 days in the spleen, and

25. Witmer, R., and Moser, R.: Sympathetic Ophthalmia and Measles, Ophthalmologica **121**:175-176, 1951.

26. Laws, H. W., and Howard, R. P.: Sympathetic Ophthalmia Successfully Treated with ACTH, Canad. M. A. J. **64**:530-531 (June) 1951.

27. Woods, A. C.: Ophthalmology's Stake in Brucellosis, Tr. Am. Acad. Ophth. **56**:616-624 (July-Aug.) 1951.

28. Spink, W. W.: Human Brucellosis, Tr. Am. Acad. Ophth. **56**:625-626 (July-Aug.) 1951.

29. Ruchman, I., and Fowler, J. C.: Localization and Persistence of Toxoplasma in Tissues of Experimentally Infected White Rats, Proc. Soc. Exper. Biol. & Med. **76**:793-796, 1951.

11 days in the lungs. They were found less regularly after these periods, being noted for 10 weeks in the liver and lungs and for 2 weeks in the spleen. Toxoplasmas appeared in the brain in four days and were uniformly present thereafter for two years, the longest interval of time at which this tissue was examined. Cowen and Wolf,[30] in a series of experiments on infection of animals with Toxoplasma, demonstrated that toxoplasmosis can be transmitted to mice by the introduction of the organisms into the vagina. Many of the mice so infected remained free of signs of disease, while a few showed some neurologic or respiratory disturbance. Pregnant mice frequently died in the terminal stages of pregnancy or shortly after parturition. The authors point out the high susceptibility of the pregnant mouse to toxoplasmosis, and to them this suggests a possible explanation of the higher incidence of congenital than of postnatal human toxoplasmosis. In a second paper,[31] they demonstrate that the organisms in pregnant mice infected with Toxoplasma by the vaginal route extend to the placentas and fetuses in utero. Placental lesions were observed in mice infected with Toxoplasma in this manner between the third and the ninth day of pregnancy. The lesions consisted of foci of necrosis in the trophoblast; the organism presumably gained access from this site to the fetal circulation. Toxoplasmas could be demonstrated in suspensions of fetal tissues on and after the 17th day by injection into normal test animals. No lesions of toxoplasmosis, or toxoplasmas, were observed in histologic sections of fetuses 11 to 21 days old removed at autopsy from mothers infected through the vagina. It was concluded that before birth the parasites were confined to the fetal blood. In a third paper,[32] dealing with the incidence and manifestations of toxoplasmosis in the offspring of mice infected by the vaginal route, it was observed that some of the young mice were retarded in postnatal development and others became ill or died during the second or fourth week of life. The majority remained symptom-free in spite of the presence of toxoplasmic lesions, of varying degrees of severity. Congenital toxoplasmosis developed only in the offspring whose mothers had been infected on the seventh to the ninth day of pregnancy. The highest incidence of congenital infection (57.6%) was obtained by giving two vaginal instillations of Toxoplasma-infected mouse brain on the eighth and ninth days of pregnancy. Mice infected before the seventh day exhibited placental toxoplasmosis but rarely delivered viable young. When the mother was infected after the ninth day, the offspring were apparently normal. In a fourth report,[33] the genital and secondary lesions in the mouse infected with Toxoplasma by the vaginal route are described. After inoculation primary inflammatory lesions developed in the vaginal wall of mice three to five days after the introduction of Toxoplasma-infected material. After a further interval of six to eight days specific focal inflammatory and necrotizing

30. Cowen, D., and Wolf, A.: Experimental Congenital Toxoplasmosis: I. The Vagina as a Portal of Entry of Toxoplasma in the Mouse, J. Exper. Med. **92**:393-402 (Nov.) 1950.

31. Cowen, D., and Wolf, A.: Experimental Congenital Toxoplasmosis: II. Transmission of Toxoplasmosis to the Placenta and Fetus Following Vaginal Infection in the Pregnant Mouse, J. Exper. Med. **92**:403-416 (Nov.) 1950.

32. Cowen, D., and Wolf, A.: Experimental Congenital Toxoplasmosis: III. Toxoplasmosis in the Offspring of Mice Infected by the Vaginal Route: Incidence and Manifestations of the Disease, J. Exper. Med. **92**:417-429 (Nov.) 1950.

33. Cowen, D., and Wolf, A.: Experimental Congenital Toxoplasmosis: IV. Genital and Secondary Lesions in the Mouse Infected with Toxoplasma by the Vaginal Route, J. Neuropath. & Exper. Neurol. **10**:1-15 (Jan.) 1951.

lesions appeared in distant organs, most constantly the central nervous system, lungs, and heart. In a fifth article,[34] the authors observe that in the offspring of infected mothers the central nervous system was almost invariably affected, the lungs only slightly less often, and the heart and other tissues inconstantly or not at all. The histopathologic changes resembled those observed in human congenital toxoplasmosis. It was also found that Toxoplasma sometimes persists in the brain for long periods, in one instance up to 78 days. Many of the young animals with congenital toxoplasmosis were subject to an unusual form of hepatic degeneration, characterized by fatty infiltration, atrophy, and necrosis of the liver cells in a pattern involving the free margins and adjacent portions of the surface. Matheson and associates[35] report the first known case of toxoplasmosis in Norway. This case, that of a man aged 38, was characterized by chorioretinitis. The disease responded to quinacrine (atabrine®) therapy. Serologic reactions were positive. Verlinde and Makstenieks[36] examined the sera of 600 persons for evidence of toxoplasmosis. In 64 sera, the dye-test titer ranged from 1:100 to 1:8,192, and the complement-fixation titer varied from 1:2 to 1:256. In four infants having congenital toxoplasmosis the organism was isolated from ventricular fluid and from the blood on several occasions during the first few months of life. The author confirmed the observations of Sabin that the complement-fixing antibody rises several weeks after onset of the disease and reaches a peak during the second month. The treated patients did not respond to sulfamethylpyrimidine. Two of the patients died, and typical histologic changes were observed. Campbell and Glifton[37] report a family of a mother, a son, and a daughter who had exhibited an intermittent maculopapular rash, conjunctivitis, and recurrent headaches for most of their lives. They also exhibited chorioretinitis and nerve deafness and had a history of meningoencephalitis. Toxoplasma dye-test titers varied from 1:32 to 1:128, and the complement-fixation test gave a positive reaction in a dilution of 1:16. The son and daughter gave positive reactions to Toxoplasma skin tests. The son had a febrile reaction, with eosinophilia and pleocytosis in the cerebrospinal fluid. The disease resisted treatment with streptomycin, penicillin, aureomycin, emetine, and sulfonamides. The titers observed in these cases were not of a magnitude that would make possible a positive diagnosis of toxoplasmosis. In the absence of isolation of parasites from these cases the diagnosis must be considered in doubt. Ström[38] reports the occurrence of toxoplasmosis in two patients as the result of a laboratory infection. The first patient was a woman aged 22 who had sudden onset of a painful swelling of the neck, pain over the eyes and forehead, and a temperature

34. Cowen, D., and Wolf, A.: Experimental Congenital Toxoplasmosis: V. Lesions in the Offspring of Mice Infected with Toxoplasma by the Vaginal Route; Observations on an Associated Hepatic Injury, J. Neuropath. & Exper. Neurol. **10**:142-157 (April) 1951.

35. Matheson, K.; Thjøtta, T., and Steen, E.: Toxoplasmic Chorioretinitis: Report of First Known Case of Toxoplasmosis in Norway, Tidsskr. norske lægefor. **71**:111-112 and 128, 1951.

36. Verlinde, J. D., and Makstenieks, O.: Repeated Isolation of Toxoplasma from the Cerebrospinal Fluid and from the Blood, and the Antibody Response in 4 Cases of Congenital Toxoplasmosis, Antonie van Leeuwenhoek, Nederl. tjdschr. hyg., microbiol. en serol. **16**:366-372, 1950.

37. Campbell, A. M. G., and Glifton, F.: Adult Toxoplasmosis in One Family, Brain **73**:281-290, 1950.

38. Ström, J.: Toxoplasmosis Due to Laboratory Infection in 2 Adults, Acta med. scandinav. **139**:244-252, 1951.

of 38.6 C. The following day there were chills, and the temperature became higher. Examination showed a fairly pronounced lymphadenopathy along the sternocleidomastoid muscles. Two days later maculopapules developed on the trunk and remained for over one week. The conjunctivitis persisted. The patient had been handling live Toxoplasma in the laboratory prior to the development of the illness but had no history of accidental inoculation. The dye-test titer rose to 1 : 4,000 two weeks after onset of the disease. The second patient, a woman aged 22, was working with Toxoplasma in a laboratory and infected herself by pricking her finger with a needle. Three days later she had a fever for one day and exhibited localized lymphangitis and lymphadenitis in the axilla. These lesions gradually subsided. Reactions to the early dye tests were negative, but after two weeks the titers became elevated to 1 : 2,000. The patient showed no other signs of the disease and made an uneventful recovery.

Steen [39] found aureomycin to be effective in the treatment of acute toxoplasmosis in experimentally infected white mice. The aureomycin resulted in a carrier state, and the mice were immune to new infections. The drug was effective if its use was commenced within 48 hours after inoculation. These observations are in contrast with the results of a number of experimental studies which have been published in this country to the effect that aureomycin does not inhibit experimental toxoplasmosis. Mohr and Westphal [40] found that the dye-test antibodies diminished in active toxoplasmosis which was treated with aureomycin.

Coccidioidomycosis.—Previous cases of conjunctivitis, lesions of the eyelid, and episcleritis have been described in association with primary coccidioidomycosis (valley fever) and with disseminated coccidioidomycosis. Lovekin [41] reports the only proved case of disseminated coccidioidomycosis in which ocular lesions were observed in the fundus. A white woman aged 30 had a four-month history of chills, fever, weakness, malaise, shortness of breath, and cough. She had previously come from Arizona to live in New York. The spherules of Coccidioides immitis were found in a granuloma which was removed from the upper lip. The precipitin test gave a negative reaction, but the complement-fixation test gave a positive reaction in 1 : 32 dilution. While the patient was extremely ill, the fundi were examined. The right fundus showed two large circular areas of exudate along the upper and lower temporal vessels ½ disk diameter from the optic nerve. A hemorrhage lay along each exudate. In the left eye a similar exudate and hemorrhage lay along the upper temporal vessels. The optic nerve was normal. It was concluded, despite the absence of histologic examination of the eye, that the clinical findings strongly suggested the diagnosis of coccidioidomycosis.

Miscellaneous Causes of Uveitis.—In their report Brooks and Fineberg [42] discuss the incidence of the ocular manifestations of typhus on the basis of a review

39. Steen, E.: Acute Experimental Toxoplasmosis Treated with Aureomycin, Acta path. et microbiol. scandinav. **27**:844-850, 1951.

40. Mohr, W., and Westphal, A.: Clinical Observations and Therapy of Toxoplasmosis, Med. Klin. **45**:1-6 (Sept.) 1950.

41. Lovekin, L. G.: Coccidioidomycosis: Report of a Case with Intraocular Involvement, Am. J. Ophth. **34**:621-623 (April) 1951.

42. Brooks, F., and Fineberg, R.: Ocular Manifestations of Typhus Fever, Am. J. Ophth. **34**:605-608 (April) 1951.

of the literature on typhus between the years 1867 and 1943. It was found that uveal complications occur in typhus in from 1 to 2% of cases; uveitis occurred in 26 of 2,031 cases reported. Fanta [43] discusses the ocular histology in typhus exanthematicus. Two eyes were removed during the 11th day of the disease. The principal histologic changes were small perivascular infiltrates around all the vessels of the eye with some areas of thrombosis. These changes were occasionally associated with necrosis of the retina. Alteration occurred in the pigment epithelium of the retina at the macular region, and the vitreous was detached in both eyes. A cellular infiltration was seen in the optic-nerve septums but never within the nerve bundles. Magee [44] described 4 instances of ocular involvement among 52 cases of relapsing fever.

A number of articles have appeared on the ocular complications in leptospirosis. Doret and Roehm [45] describe eight cases of leptospirosis. Leptospira canicola seems to be the organism which most frequently causes ocular complications. Three of the patients had ocular signs in infections with Lept. canicola; four, in infections with Lept. pomona, and one in infections with Lept. australis. In three of the eight cases the agglutinin reaction of the aqueous humor, as well as that of the blood, was positive. Two of the patients showed papilledema, which could be due to meningitis. Six patients showed severe iridocyclitis, which was benign and which healed without complications. Rarely, a chronic form of iridocyclitis may occur and be accompanied with dense vitreous opacities. The following species of living leptospiras should be used as antigens: Lept. icterohaemorrhagiae; Lept. canicola, Lept. ballum, Lept. grippotyphosa, Lept. bataviae, Lept. saxkoebing, and Lept. pomona.[46] The authors describe a case of acute "influenza" which developed in a young man 10 days after he commenced work in a slaughterhouse. Seven months later left iridocyclitis developed, which lasted approximately a month. A high titer of agglutinins against Lept. pomona was obtained. The authors point out that the diagnosis of leptospiral iridocyclitis may be presumptive and based on serologic findings unless organisms can be isolated from the blood. Beleke and Bandau [47] describe two cases of leptospirosis accompanied with bilateral iridocyclitis. The diagnosis was based on the positive reaction to the complement-fixation test. They point out that ocular complications are rare in infection with Lept. canicola, but if they occur the prognosis is usually good.

Rheumatoid Arthritis.—Vesterdal and Sury [48] discuss iridocyclitis and band-shaped corneal opacity in juvenile rheumatoid arthritis. The eyes were found to be

43. Fanta, H.: Ocular Histology in Typhus Exanthematicus, von Graefes Arch. Ophth. **151**:735-743, 1951.

44. Magee, G. R.: Ocular Complications of Relapsing Fever, Tr. Pacific Coast Oto-Ophth. Soc. **31**:163-170, 1950.

45. Doret, M., and Roehm, A.: Ocular Complications in Benign Leptospiroses, Klin. Monatsbl. Augenh. **118**:51-55, 1951.

46. Beeson, P. B.; Hankey, D. D., and Cooper, C. F., Jr.: Leptospiral Iridocyclitis, J. A. M. A. **145**:229-230 (Jan. 27) 1951.

47. Beleke, H., and Bandau, R.: Ocular Complications in Canicola Fever, Deutsche med. Wchnschr. **76**:729-730 (June) 1951.

48. Vesterdal, E., and Sury, B.: Iridocyclitis and Band-Shaped Corneal Opacity in Arthritis, Acta ophth. **28**:321-327, 1950.

affected in 21% of 161 children with juvenile rheumatoid arthritis observed between 1920 and 1949. In older children the iridocyclitis was acute or subacute and gradually became chronic. In young children the disease apparently was chronic from the outset. Forty-five per cent of the children recovered completely, and 21% had bilateral reduction of vision below 6/36. Wagener [49] reviews the literature and reports one case of iritis with zonular degeneration of the cornea as a symptom of multiple rheumatoid arthritis (Still's disease) in children. The author thinks that the corneal band-shaped dystrophy is due to a rheumatoid vascular disturbance with major localization in the region of the lid aperture.

In another article [50] is reported the investigation of the antistreptolysin and antistaphylolysin titers in patients with acute iridocyclitis. The authors point out that measurable serum antibody (antistreptolysin) is formed against the hemolytic toxin (streptolysin) which is produced by streptococci. All the commonly occurring streptococci pathogenic to man in Lancefield's groups A, C, and G produce a hemolysin which is antigenic in the free state. In patients with streptococcic infections, such as tonsillitis, erysipelas, and scarlet fever, the titer becomes elevated. The titer is also found to be raised in 80 to 100% of patients with acute rheumatism. The authors measured the titers of the sera of 105 patients with acute iridocyclitis of doubtful origin. Patients were excluded who during the previous six months had had a streptococcic or staphylococcic infection. The titers were then compared with those of the sera of a control group of 552 blood donors. The staphylolysin titer did not differ in the two groups. The titer for antistreptolysin was raised in patients with iridocyclitis, averaging 119.90 ± 60.60 per milliliter, as compared with that for the control group, which measured 74.20 ± 54.20 per milliliter of serum. These figures were considered statistically significant, since the chance was less than 1 : 1,000,000 that, with respect to antistreptolysin titers, patients should represent a normal material selected at random. The study suggests that infections due to hemolytic streptococci may be of importance in the etiology of acute iridocyclitis.

Reiter's syndrome may be accompanied with uveitis, as well as conjunctivitis. Ogryzlo and Graham [51] report three cases of this syndrome, without ocular changes, in which the condition responded rapidly to treatment with corticotropin. Withdrawal of the hormone was followed by a relapse, which was mild in two patients and severe in one. Two of the patients eventually recovered completely; the third was treated with cortisone after the relapse, with striking relief of symptoms. In another article [52] it is stated that in France Reiter's syndrome is usually associated with rheumatic fever and is called the "conjunctival-urethral-synovial syndrome of Fiessinger-Leroy." In France dysentery and intestinal infections, as well as rheumatism, tuberculosis, and allergy, have been encountered as causes of this syndrome.

49. Wagener, F.: Zonular Degeneration of the Cornea and Iritis as a Symptom of a Special Form of Arthritic Rheumatism in Children (Still's Disease), Klin. Monatsbl. Augenh. **117**:161-168, 1950.

50. Schöne, R., and Steen, E.: Antistreptolysin Titre and Antistaphylolysin Titre in Iridocyclitis Acuta, Acta ophth. **29**:201-211, 1951.

51. Ogryzlo, M. A., and Graham, W.: Reiter's Syndrome: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone, J. A. M. A. **144**:1239-1243 (Dec. 9) 1950.

52. Maignien-Courard: Ocular Symptoms as a Particular Feature of Acute Rheumatic Fever: Fiessinger-Leroy and Reiter's Syndrome, Ann. ocul. **183**:660-683, 1950.

Harada and Vogt-Koyanagi Syndrome.—An atypical case of the Vogt-Koyanagi syndrome is described by Stern.[53] The patient had an acute onset of severe diffuse uveitis associated with a nerve type of hearing loss, alopecia areata, and pleocytosis. Poliosis and vitiligo were absent. Cowper [54] describes a case of this syndrome and suggests the name "uveoencephalitis." His patient exhibited severe meningitis, bilateral retinal detachment, and severe fulminating anterior uveitis. The author objects to the classification of Vogt-Koyanagi syndrome and Harada's disease as separate clinical entities, citing cases from the literature in which manifestations common to both have been reported. Most observers who are familiar with this condition are in entire agreement with the conclusions.

Heterochromic Cyclitis.—Matteucci [55] discusses the two forms of heterochromia of the iris: the Fuchs type, which is characterized by a slow, progressive degeneration, and an inflammatory type, in which the iris gradually becomes paler, with semidilated and poorly reacting pupil. In the Fuchs type there are usually a slight aqueous flare, keratic precipitates on the corneal and lens capsule, and occasional hypertension or hypotension. The sympathetic, or simple, type of heterochromia is self-limited and follows an injury or an inflammation of the sympathetic nervous system on the same side as the affected eye. Examination shows constriction of the pupil and evidence of Horner's syndrome. The irritative phenomena in this form are of short duration, and the progression is limited. Toselli and Heer [56] studied the cytologic changes in the aqueous humor under experimental conditions. Excision of the superior cervical ganglion on one side caused Horner's syndrome without change in the cytologic elements of the aqueous humor. The Pandy reaction of the aqueous humor always remained negative. Partial ligature of the left superior cervical ganglion caused mydriasis, and the cytologic elements of the aqueous humor remained normal and Pandy's reaction negative. Retrobulbar injection of alcohol caused an increase in the cellular contents of the aqueous humor. Lymphocytes were the cells most commonly noted in these eyes.

Passow [57] discusses the role of the sympathetic nervous system in growth and pigmentation, commenting on status dysraphicus and its ocular manifestations, with special reference to heterochromia. He found that Horner's syndrome combined with heterochromia and associated partial atrophy of the face and breast on the same side is most probably due to status dysraphicus. Any of these symptoms can frequently be found in members of the same family and in the same generation. In the author's experiments on rabbits, in which the cervical ganglionic chain was cauterized, a retardation in formation of pigment was found when the animal was

53. Stern, R.: Vogt-Koyanagi Syndrome: Report of an Atypical Case, Am. J. Ophth. **34**:105-107 (Jan.) 1951.

54. Cowper, A. R.: Harada's Disease and Vogt-Koyanagi Syndrome, A. M. A. Arch. Ophth. **45**:367-376 (April) 1951.

55. Matteucci, P.: Pathologic Considerations of Fuchs's Heterochromia, Ann. ocul. **184**:385-403 (May) 1951.

56. Toselli, C., and Heer, G.: Cytologic Changes in the Aqueous Humor in Experimental Conditions, Rass. ital. ottal. **19**:392-397, 1950.

57. Passow, A.: Role of Sympathetic Nervous System in Growth and Pigmentation: Contribution on Status Dysraphicus and Its Ocular Manifestations, with Special Reference to Heterochromia, Klin. Monatsbl. Augenh. **116**:561-578, 1950.

very young. Status dysraphicus most frequently affects the cervical sympathetic chain but may extend toward the brain and cause bulbar symptoms, such as lesions of the fifth, sixth, and seventh cranial nerves.

Virus Uveitis.—Evans and Moore [58] inoculated the rabbit eye with the virus of herpes simplex and observed that all the neural elements of the retina, the fibroblasts, the radial and circular muscle cells of the iris, the muscle cells of the ciliary body, the pigmented and nonpigmented epithelium of the ciliary body, and macrophages contained the nuclear inclusions of this virus. The endothelium was not found to contain virus particles. The virus of feline agranulocytosis affected fibroblasts, bipolar cells, and pigment epithelium of the visual retina and ciliary body in experimentally infected cat eyes. This virus caused a severe, and often fatal, systemic infection after intraocular inoculation. External examination of the eyes, however, showed only minimal evidence of the infection. Ornithosis virus injected in large doses into the eyes of three rabbits caused a violent infection, with conjunctival exudate, thickening and opacification of the cornea, and acute inflammation of the tissues near the chamber angle. Inclusion bodies were found in macrophages, fibroblasts, and a small number of endothelial cells on the inner surface of the cornea. It was suggested that the important factor in the pathogenesis of the severe corneal edema was the toxicity of the virus, which was released into the anterior chamber from infected cells. Damage to the endothelium resulted in increased permeability. Pasca [59] employed influenza A and influenza B virus, injecting 0.5 ml. of infected rat lung into the cornea of 15 rabbits and 10 other animals. Examination of the eyes showed the uveal tract and the optic nerve to be most seriously affected. There was an abundant lymphocytic and fibrinous exudate on the iris and ciliary body. The uvea showed large hemorrhages, which are characteristic of lesions due to the influenza virus. According to the authors, these experimental findings explain the frequency of postinfluenzal uveitis and glaucoma, especially hemorrhagic glaucoma. Cavara [60] furnished a complete review of present knowledge of uveal inflammations which are caused by viruses. Houral [61] describes the case of a man aged 42 who had epidemic hepatitis accompanied with polyneuritis and glomerulonephritis. Approximately 30 days later bilateral iridocyclitis developed, gradually disappearing within 14 days.

The etiologic factor in the ocular-mucous membrane syndrome, or recurrent uveitis, has not definitely been established. Some authors consider it to be a virus infection, while others consider it to be due to the L bacillus of the pleuropneumonia group. This syndrome was first described by Adamantiadis, in 1930. Behçet drew the various manifestations of this syndrome together in 1937, so that it became recognized as a clinical entity, which is frequently described as Behçet's triple-complex syndrome. The triple complex consists of oral ulceration, genital ulceration, and various ocular lesions, ranging from conjunctivitis and iritis to thrombosis

58. Evans, C. A., and Moore, G. E.: Effects of Viruses on Intraocular Tissues: II. Infections with the Viruses of Herpes Simplex, Feline Agranulocytosis and Ornithosis, J. Infect. Dis. **87**:1-9 (July-Aug.) 1950.

59. Pasca, G.: Further Experimental Research on Action of the Influenza Virus on the Ocular Tissues, Boll. ocul. **29**:396-404, 1950.

60. Cavara, V.: Uveal Inflammations Caused by Filtrable Viruses, Boll. ocul. **29**:3-28, 1950.

61. Houral, V.: Neurologic Complications in Epidemic Hepatitis, Casop. lék. česk. **89**:1402-1404, 1950.

of the central retinal vein. Thrombophlebitis of the veins of the extremities has recently been observed in this syndrome. Gray [62] reports such a case in a man aged 26. After a long period of general symptoms accompanied with cutaneous and articular phenomena, the patient had thrombosis of the superior temporal branch of the right retinal vein with many vitreous opacities. Various cranial- and spinal-nerve paralyses developed later; still later bilateral iridocyclitis occurred. Thrombosis of some of the cranial vessels finally caused the patient's death. Adamantiadis [63] describes an additional case and notes that he has now observed a total of six cases. He comments on the great irregularity in the time at which various elements of this syndrome appear. Frequently iritis or thrombophlebitis is the presenting symptom. He stresses the protracted course of the disease.

Focal Infection as a Cause of Uveitis.—François [64] discusses the importance of the dental origin of uveitis. He comments that in two-thirds of the cases of uveitis it is not possible to determine the cause. He describes the two possible means by which a dental focal lesion may affect the eye. In the first type, a primary infection spreads via the blood stream directly to the eye and sets up a low-grade secondary infection. In the second type, a focal ocular reaction occurs after a period of sensitization to the microbes causing the dental infection. The teeth of the superior maxilla on the same side as the affected eye, especially the molars and the premolars, are most likely to cause the ocular lesions. Certain factors speak against the dental origin of uveitis. Among these are the large number of people who have focal inflammatory processes in the teeth and the rarity with which these produce uveitis. Frequently, in any one patient other infections, such as tuberculosis, syphilis, or rheumatism, may also be the cause of the uveitis. Extraction of teeth often does not cure the uveitis. Of the author's 221 cases of unilateral acute iridocyclitis, the cause was undetermined in 72%. Of those in which it could be determined, syphilis, gonorrhea, diabetes, and rheumatism were the principal causes. Of 111 patients with bilateral acute iridocyclitis, the cause was undetermined in 61%. Syphilis, gonorrhea, diabetes, and rheumatism accounted for the condition in those patients in whom it could be determined. Of 73 patients with unilateral chronic uveitis, the cause was undetermined in 67%. Tuberculosis was by far the commonest cause of the disease. Of 116 patients with bilateral chronic uveitis, the cause was undetermined in 65%, and tuberculosis accounted for the disease in most of the cases in which it could be determined. One hundred thirty-three patients exhibited dental lesions which could be expected to be a possible focus; 52 patients showed dental lesions which might be the sole cause of the iridocyclitis. In 41 of these 52 patients the infection was located within the tooth or at the apex.

Treatment of Uveitis.—Most of the articles dealing with treatment during the past year have been concerned with the effects of corticotropin and cortisone in experimental infections, as well as in the clinical disease. Biegel [65] studied the effect of cortisone on horse-serum uveitis in rabbits. In his study the uveitis was produced

62. Gray, G. S.: Triple Complex Syndrome of Behcet, Canad. M. A. J. **62**:597-599 (June) 1950.

63. Adamantiadis, B.: Recurrent Uveitis: A New Case of a Complex Syndrome, Am. J. Ophth. **34**:447-449 (March) 1951.

64. François, J.: Importance of Dental Etiology in Uveitis, Ann. ocul. **183**:745-770, 1950.

65. Biegel, A. C.: Effect of Cortisone on Horse Serum Uveitis in Rabbits, A. M. A. Arch. Ophth. **45**:258-273 (March) 1951.

by intravitreal injection of horse serum in previously sensitized rabbits. Treatment was carried out by systemic administration of cortisone. The histologic and clinical effects were assessed. The studies revealed that the rabbits treated with cortisone exhibited a milder uveitis than did the controls. The animals treated with cortisone exhibited only a very slight vitreous haze, whereas the vitreous of the controls eventually became cloudy. Histopathologically, the eyes of the cortisone-treated rabbits showed considerably less inflammatory reaction than did the control eyes. The data indicated that the precipitin titers of the cortisone-treated rabbits were high despite the administration of cortisone, although they were possibly lower than those of the controls. It seemed to the author that the beneficial effect of cortisone on the uveitis was due to inhibition of the inflammatory reaction rather than to prevention of the reduction of the systemic hypersensitivity to horse serum. In another article,[66] the role of the adrenal cortex in the treatment of ocular diseases with pyrogenic substance is investigated. It was found that the intravenous injection of foreign protein results in a decrease in the circulating eosinophiles in the blood. This was thought to be due to the shock reaction, which stimulated the production of adrenal steroids. The maximal eosinopenia occurred about 18 hours after the injection. Patients who were refractory to foreign protein showed no decrease in the circulating eosinophiles. Spies and Stone [67] selected six patients with various diseases who had failed to respond to the use of three distinct antihistaminic substances. Two of these patients had rheumatoid arthritis with rheumatoid uveitis. Those with rheumatoid uveitis responded promptly to the local use of ophthalmic ointment containing 25 mg. of cortisone acetate per gram. The ointment was applied every 30 minutes during the working day for six days. Mosher [68] used cortisone by subconjunctival injection and as a collyrium in a group of 53 patients with various types of ocular disease. The local use of cortisone was found to be more effective in diseases of the anterior segment than in diseases of the posterior segment of the globe. One-fourth of the patients with uveitis failed to respond to the local use of cortisone. In another study,[69] four of six patients with acute iritis responded promptly to the topical application of cortisone. The authors found that topical use of cortisone in chronic iridocyclitis may be of great value in preventing the relapses which so commonly occur. Koff and co-workers [70] report the effects of subconjunctival injection of cortisone in iritis. The authors anesthetized the conjunctiva with tetracaine hydrochloride and then applied a pledget of 10% cocaine hydrochloride to the bulbar conjunctiva at the site of the injection, usually near the 12 o'clock meridian, 5 to 6 mm. from the upper limbus. Two-tenths to 0.4 cc. (25 mg. per cubic centimeter) was then injected subconjunctivally

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with a 23-gauge needle. Subsequent injections were given as indicated, the procedure being repeated in 48 or 72 hours, if necessary. They found that eight of nine patients with acute or acute recurrent iritis showed decided improvement with this method of treatment. In three patients with chronic uveitis who had been benefited by corticotropin therapy, an exacerbation developed after cessation of its use. The relapse was controlled by one injection of cortisone every two to three weeks. In three cases of chronic granulomatous uveitis the disease was unaffected by systemic administration or topical use of cortisone. Olson and co-workers [71] treated a large group of patients with ophthalmic diseases with both corticotropin and cortisone parenterally. The largest group of patients studied were those with acute inflammation of the anterior uveal tract. Thirteen patients with iridocyclitis were considered severely ill. In all 13 patients the relief of pain and photophobia was rapid. Seven of the patients were treated with corticotropin and six with cortisone. In none of the eyes was a flare present after 48 hours; in 3 patients the anterior chamber was free of cells within 3 days, while in the other 10 patients it cleared in from 4 to 12 days. In the group treated with corticotropin there had been but one recurrence, and the patient was then treated with cortisone, responded rapidly, and had been free of activity for 17 days. Five patients with choroiditis were treated with corticotropin and cortisone, and all responded well to therapy. Two patients with acute diffuse uveitis were treated. Both showed rapid improvement in the first three days and continued improvement during the period of treatment. Five patients with chronic iridocyclitis were treated with corticotropin. Four of these had bilateral, and one unilateral, inflammation. The response was gradual but definite. In two patients the resolution was complete at the conclusion of treatment, and the other three retained minimal signs. Each patient had a recurrence to approximately the pretreatment level within a period of one to two weeks. Two patients with central chorioretinitis were treated. No appreciable change was observed in the size or color of the lesions, although the visual acuity and central visual fields showed notable improvement. Within a week after withdrawal of therapy the lesions were again active, with superficial hemorrhages, edema, and extension toward the macular area. One patient with chronic posterior uveitis was treated with corticotropin. There was gradual improvement during the course of therapy, but after withdrawal the lesion again became active. Fitzgerald and co-workers [72] report the early clinical results of corticotropin and cortisone therapy of ocular disease. The daily dose of corticotropin ranged from 40 to 75 mg., and the therapy was continued from 7 to 10 days. Cortisone was most frequently given in daily injections of 100 mg. for an average of 10 days. A total of 198 patients with ocular disease were treated with these agents. Of these, 106 had either anterior or posterior uveitis. The acute uveal inflammation exhibited the best response to both corticotropin and cortisone, the drugs producing rapid, dramatic subsidence of symptoms and signs. The remission of the ocular manifestations was sustained in most instances. The results of local administration of cortisone in a

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number of the reported cases compared favorably with those of the systemic use of corticotropin and cortisone. Chronic uveal inflammations responded less well than the acute types. These observations are substantiated in another report,[73] in which it is determined that chronic ocular inflammations respond less well to corticotropin and cortisone than do acute ones. Furthermore, a relapse is more likely to occur after withdrawal of treatment in chronic than in acute lesions. Other reports [74] attest to the successful treatment of uveal disease with cortisone. Scheie and co-workers [75] report the results in 36 patients treated systemically with cortisone and corticotropin. Six patients with focal choroiditis were treated parenterally—three with corticotropin and three with cortisone. All the patients with fresh lesions seemed to benefit from treatment. Four patients having diffuse granulomatous uveitis were treated, and all responded poorly. A patient presenting the classic signs of severe Harada's disease did not respond to treatment. Topical application of cortisone was used in the treatment of 68 eyes with various types of ocular disease. Three patients with acute iridocyclitis gave an encouraging response. One patient with phacoanaphylactic endophthalmitis received some benefit. Another patient, with retained lens material after an attempted intracapsular cataract extraction, was treated with topical application of cortisone ofter the development of severe iridocyclitis; the results were encouraging. Twelve eyes with chronic granulomatous posterior uveitis without focal choroidal lesions were treated, without improvement. Harvey and co-workers [76] treated eyes with nongranulomatous iritis, sympathetic ophthalmia, tuberculous uveitis, and other ocular diseases with corticotropin and cortisone. The first patient had acute nongranulomatous iritis and was treated with corticotropin. The inflammatory reaction subsided promptly with use of this hormone. Eight months later a recurrence was treated successfully with cortisone. The second patient had rheumatoid arthritis with development of acute rheumatoid uveitis. She was treated with parenteral injections of cortisone; the lesions responded promptly. In a case of sympathetic ophthalmia corticotropin produced immediate clearing of the inflammatory phases of the disease. A relapse occurred during treatment, but after a period of rest corticotropin was again used, with subsidence of symptoms. At the termination of treatment there was only a minimal inflammatory reaction. Corticotropin therapy was used in an additional case of sympathetic ophthalmia; improvement was noted within 24 hours after the beginning of therapy and was steadily maintained during treatment; a relapse did not occur. In a third case of sympathetic ophthalmia cortisone was used topically; after 10 days the eyes were completely free of all evidence of inflammation. In a case of tuberculous iridocyclitis the disease responded to corticotropin therapy, and on two occasions on which the dose was reduced the inflammation recurred.

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In a second case of tuberculous iridocyclitis improvement was rapid on treatment with fairly large doses of corticotropin. In an additional case of tuberculous iridocyclitis cortisone resulted in considerable improvement in the inflammatory disease in the eye and reduction of the intraocular pressure. In two cases of uveitis following herpes zoster ophthalmicus remarkable improvement occurred within a day after the local application of cortisone. When treatment was discontinued, there was a recurrence of the inflammatory reaction, which again responded promptly to resumption of treatment. Kellerman [77] treated a series of patients with uveitis by administration of pregnenolone in a dose of 100 mg. three times a day for one to two weeks. Eight patients were treated. Two additional patients were treated with 100 mg. given intramuscularly once a day. The uveitis was unaffected by pregnenolone therapy.

TRAUMATIC LESIONS

Cohen [78] reports a case of a traumatic iris cyst following probable implantation of a glass foreign body in the ciliary area of one eye. The cyst developed over a long period and eventually resulted in an attack of acute glaucoma, 45 years after the injury. A pearl cyst of the iris following a perforating injury of the eye in which two lashes were carried into the anterior chamber is reported.[79] The cyst developed eight months after removal of the cilia and in a position remote from the original location of the cilia. The cyst was successfully removed by iridectomy through a corneal incision.

VASCULAR AND DEGENERATIVE DISEASES

Zollinger [80] studied the occurrence of vascular proliferation on the anterior surface of the iris in eyes removed for various causes. Seventy-two eyes were studied. All 20 eyes with hemorrhagic glaucoma occurring after thrombosis of the central retinal vein and 10 eyes with glaucoma accompanied with total retinal separation showed a typical neoformation of vessels on the iris. In 6 of 16 cases of absolute primary glaucoma similar changes were noted, and in all the 6 cases there were many retinal hemorrhages, due to hypertension. Nine cases of secondary glaucoma due to chronic iridocyclitis were observed; new-formed vessels were noted in three cases, but in all of these three a retinal separation was present. Seventeen patients with perforating injury were examined at least three months after the perforation; 5 patients without retinal detachment showed no changes in the iris, but of the 12 with total detachment, 6 had new-formed vessels on the iris. These findings indicate that thrombosis of the central retinal vein and retinal detachment, if associated with secondary glaucoma, may produce identical morphologic changes on the surface of the iris. Klien [81] studied the origin of macular lesions due to vascular

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81. Klien, B. A.: Macular Lesions of Vascular Origin, Am. J. Ophth. **34**:1279-1289 (Sept.) 1951.

disease and distinguished them from primary degenerative lesions and from inflammatory processes. She was able to demonstrate that the vascular changes which cause macular lesions may occur in the choroidal vessels or the retinal vessels or in both systems simultaneously. Secondary senile degeneration is due to primary focal arteriosclerosis of the choroid, resulting in atrophy of the choroidal stroma and rarefaction and atrophy of the choriocapillaris. These changes cause damage in the pigment layer and the neuroepithelium of the retina. The author stresses the differential diagnosis of secondary senile macular degeneration and senile primary heredodegenerations. Senile macular lesions not infrequently reach a considerable size and result in destruction of the retinal pigment epithelium, allowing a view of the greatly sclerosed choroidal vessels. This is not as commonly observed in primary degenerations. In secondary degenerations there is a close correlation of the objective and the subjective findings, whereas in heredodegeneration the discrepancy is often striking. Histologically, in the heredodegenerations the choriocapillaris is well preserved, whereas in secondary senile degenerations considerable atrophy of the choroid and choriocapillaris are seen. Secondary senile macular degeneration may have a superimposed circinate retinopathy.

Angioid Streaks.—Kruemmel [82] reports a case with photographs, showing the development of angioid streaks. In the early stages subretinal hemorrhages were found at the site of fresh ruptures in Bruch's membrane (lamina basalis). The hemorrhages slowly disappeared, and the ruptures persisted as angioid streaks. Dixon [83] reports angioid streaks and pseudoxanthoma elasticum in the case of a Negro woman aged 29. Lesions of the central nervous system developed as a result of aneurysm formation in the carotid artery, due to involvement of the elastic tissues. Successful ligation of the internal and external carotid arteries was carried out. Anderson [84] reports three cases of angioid streaks. He stresses the macular changes which accompany the choroidal lesion. In the early stages a slowly progressing pigmentation is noted in the macular region, probably due to atrophy of the choroidal vessels. Subretinal exudates are frequently found, and these result in fibrotic changes at the macula. The exudates may be accompanied with hemorrhages in or around the macula. A large hemorrhage may be the only lesion noted. Patients in older age groups show pigmentary disturbances in the macula as the commonest lesion; in younger persons exudative changes are commoner.

Degenerative Changes.—McCulloch [85] reports the case of a white woman aged 56 who had repeated attacks of glaucoma, due to pathologic changes in the iris and choroid. The iris showed a peculiar tearing of the stroma (iridoschisis). Choroidal lesions were interpreted as multiple ruptures. Panter [86] reports two cases of iridoschisis. In the first, that of a white woman aged 62, with chronic glaucoma, iridoschisis developed in an atrophic area of the right iris two years after institution

82. Kruemmel, H.: Clinical Observations on the Development of Angioid Streaks, von Graefes Arch. Ophth. **151**:167-178, 1951.

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86. Panter, E. G.: Two Cases of Iridoschisis, Am. J. Ophth. **34**:297-298 (Feb.) 1951.

of treatment for the glaucoma. Similar changes occurred in the opposite eye. In the second case, that of a man aged 81, iridoschisis of the left iris appeared in 1946. The condition progressed and became almost total by 1949; a similar process was beginning in the right iris at this time. There was no history of uveitis or glaucoma.

Lowe [87] reports three cases of choroideremia occurring in three generations in one family. In this pedigree the condition was inherited as a sex-linked conditional dominant. Two males from alternate generations showed the disease in its dominant form, and one female in an intervening generation showed the disease in the benign form of the female transmitter.

NEOPLASMS

Snell [88] studied heterotransplantation of tumors into various regions of the guinea pig eye. The first group of studies were carried out with human-breast-carcinoma tissue removed from a cerebral metastasis. The tumor was transplanted into the anterior chamber of 194 guinea pig eyes and grew in 115, or 59%. Intracorneal injections of the tumor were made in 41 guinea pig eyes; growth occurred in 6, or 15%. None of the intravitreal or lens implants showed evidence of growth. Similar studies were made with mouse carcinoma. Of 103 transplants, 47% grew in the anterior chamber, and of 33 transplants into the cornea, 70% were regarded as takes. No takes were observed in implants into the lens and vitreous, and 11% of implants into the subconjunctiva possibly could be considered as takes. The authors required that the transplant increase in size at least threefold before it could be considered a take and that the cells of the growing transplant be the same as those transplanted.

The value of aspiration biopsy in uveal tumors is indicated by three reports.[89] In the first case it was impossible to determine clinically whether a tumor or cyst of the ciliary body and choroid was present. Aspiration was performed, and the stained material showed a malignant melanoma. The eye was enucleated and a large tumor found. In the second report aspirations of the aqueous was done in two cases of malignant melanoma of the ciliary body. The slides were stained by the Papanicolaou technique. In these cases the malignant cells in the aqueous humor of the anterior chamber and in the tumor were those characteristic of the malignant melanoma. At enucleation the diagnosis was confirmed. In the third report the authors mention the infrequency of malignant melanoma in their experience, since they had seen only 2 cases in over 100,000 patients. In those two cases the diagnosis was established by aspiration of tumor material through the upper temporal quadrant of the globe with a 23-gauge needle, the needle entering the choroidal tumor. The material was placed on a slide and stained with the

87. Lowe, R. F.: Choroideremia: A Report of 3 Cases in 3 Generations, Brit. J. Ophth. **35**:31-37 (Jan.) 1951.

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May-Grünwald Giemsa method. The authors found atypical cells with abnormal nuclei containing one to three ovoid nucleoli. The eyes were enucleated, and a typical malignant melanoma was found. Spaeth [90] made a statistical analysis of 170 cases of tumors of the eye and orbit. Malignant melanoma was found in 33 cases; among these were 5 deaths in the follow-up period. Four of these tumors occurred in the iris and ciliary body, with no deaths in the follow-up period. There were 17 choroidal melanomas, with 3 deaths, and 11 orbital melanomas with 2 deaths. Funk [91] reports an interesting tumor of the iris which was considered to be in the melanoma group, but it was not possible to determine clinically whether the tumor was benign or malignant. Consultants at two teaching centers disagreed as to whether the tumor was malignant or benign. The tumor was removed, and they disagreed also on the microscopic diagnosis. Stallard [92] reported on a 10-year follow-up observation on a patient aged 39, who had bilateral malignant melanoma of the choroid in 1939. The left eye was removed, and a positive histologic diagnosis made. The right eye was treated by sewing radon seeds over the area of the neoplasm. The tumor shrank, and 10 years later all that could be seen was a flat, pigmented area about one-eighth the size of the original lesion, surrounded by a scarred atrophic retina and choroid. The lens showed a few vacuoles at the equator and in the upper nasal quadrant; vision was normal.

Three articles deal with cases of hemangioma of the face associated with choroidal hemangioma.[93] A positive histologic picture was noted in each case.

Stanworth [94] describes the clinical and the pathologic findings in a case of leiomyoma of the iris removed by iridectomy. The outcome in this case was successful. According to the author, the clinical diagnosis of leiomyoma may be made on the following signs: (1) absence of inflammation; (2) absence of signs showing invasion of the iris; (3) presence of hyphema; (4) site of the tumor in the lower half of the iris; (5) localized cataract, and (6) absence of gross pigmentation.

Kulvin [95] reports a case of chorioepithelioma metastatic from the left testis to the left choroid. This is the fifth case of such a lesion observed in a man. The metastasis developed almost a year after removal of the testis. Death occurred two months after development of ocular symptoms.

Cooper and Riker [96] report an interesting case in which severe iridocyclitis developed in the right eye. The condition resisted all treatment, and the eye eventually became blind and was enucleated. Histologic examination showed a malignant lymphoma affecting almost the entire uveal tract. Lymphadenopathy and enlarge-

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ment of the liver, spleen, and testis developed later. The testis was removed and found to contain a lymphosarcoma. The malignant lymphoma involving the eye in this case was probably either metastatic or part of widespread disseminated lymphoid activity.

Reese [97] reports a series of spontaneous cysts of the ciliary body which simulated neoplasms. Small epithelial cysts of the ciliary body are not uncommonly observed in eyes which are examined histologically. When the cysts are large, they may manifest themselves clinically, and the differentiation from a tumor may be difficult. Microscopically, the cyst wall is usually composed of unpigmented epithelium, which may be one to four cells thick. The cavity is filled with a clear fluid, which may be partially evacuated in preparation of the specimen. When the cyst is larger and extends along the posterior surface of the iris, it often simulates a malignant melanoma because of the pigmentation of the cyst wall. The pigment in the wall interferes with transillumination, and a dark shadow is usually obtained. Important differentiating points in cases involving the iris are that the cyst protrudes from the posterior surface of the iris at its periphery, is smooth, and may be slightly tremulous.

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News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

The American Orthoptic Council.—The American Orthoptic Council announces that its annual intensive course in orthoptics will be presented in St. Louis, from July 1, 1952, through Aug. 30, 1952. The tuition is $150, $50 being payable at the time of application as a matriculation fee. The Council requires a minimum of nine months for certification, and those taking the course receive credit for two months. The remainder of the training time is spent in practical work, similar to an internship, at any one of a number of approved training places. All practical training must be completed under the supervision of an orthoptic technician who has received the Council's certificate. The Council endeavors to place all students for practical training if they have not already made such arrangements prior to taking the course. For administrative reasons, few training places will accept students for training for periods of less than nine months.

Inquiries for further information or for applications may be addressed to Richard G. Scobee, M.D., American Orthoptic Council, 640 S. Kingshighway Blvd., St. Louis 10.

SOCIETY NEWS

Florida Society of Ophthalmology and Otolaryngology.—The 13th annual meeting of the Florida Society of Ophthalmology and Otolaryngology will be held at the Hollywood Beach Hotel, Hollywood, Fla., April 27, 1952.

The following papers will be presented: President's Address, Dr. Charles Grace, St. Augustine; Present-Day Management of Chronic Suppurative Otitis Media, Dr. Arthur Juers, Miami; Ocular Neuroses, Dr. G. Tayloe Gwathmey, Orlando; Cataract Extraction by Erysiphake (moving picture), Dr. James R. Nieder, Delray Beach; Selection of Operative Procedure in Vertical-Muscle Imbalances, Dr. Edward A. Dunlap, New York; Therapeutic Approaches to the Inner Ear, Dr. Jerome A. Hilger, Minneapolis.

Election of officers follows the Scientific sessions.

Book Reviews

A Manual of Orthoptics. By Julia E. Lancaster. Price, $5.50. Pp. 199. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

This is the soundest and clearest exposition of orthoptics yet to be published and should be read by everyone who treats the child with squint.

The book is divided into two parts, the first of which deals with the philosophy of orthoptics, and the second with the application of orthoptic technique. Miss Lancaster develops in a concise and logical manner the reasons for orthoptic training and the goals to be achieved. She first summarizes the growth and development of binocular vision, treating the latter as subject to the laws which govern the development of conditioned reflexes. She then presents a concise and lucid outline of the learning process. It is interesting to find that she believes the age of readiness for orthoptic training is at about 8 years. From this it would seem that many of us are expecting too much from orthoptics at an early age, since we now endeavor to correct the squint, as a cosmetic blemish at least, by the age of 6 years.

The orthoptist as a teacher is the subject of Chapter II, which stresses the point of view that "learning is the method by which the individual adapts to his environment." The author stresses that at each step in the learning process orthoptic techniques should be planned to promote the correct responses to situations within the ability of the patient, and that after the correct responses have been achieved, adequate opportunity for repetition must be provided. Unquestionably, it is this need for repetition which has created the group called orthoptic technicians, since no ophthalmologist would have the time to carry out such training himself.

Miss Lancaster is very careful to define the proper sphere of activity of the orthoptic technician. This is very well expressed by her remarks on diagnosis, a quotation from which follows:

> . . . Ophthalmologists are beginning to realize that to the extent they delegate the function of diagnosis, they are delegating the performance of an integral part of ophthalmology, and if a technician diagnoses, she is, to that extent, practicing ophthalmology, a task for which her specialized and limited training can scarcely qualify her. Only the most serious complications in relationship can result if (*a*) the surgeon feels that the technician is usurping his function as an ophthalmologist by doing too much diagnosis, or (*b*) if he expects the technician to diagnose the surgical problem and finds that she is incompetent to do so.

Chapters IV to XI deal with the specific application of orthoptics to the various types of squint. The author stresses the importance of excluding from orthoptic procedures all patients who are definitely not suited for orthoptic help, such as those with marked pareses, congenital anomalies, and untreated amblyopias and all those who by ophthalmological diagnosis are readily classified as unable to attain binocular vision.

The relation of orthoptics to surgical treatment is well put. It is the function of surgery to place the eyes in the position where they can make the necessary binocular adjustments to insure the images falling on corresponding retinal points, i. e., on the two maculae. The patient who has had a satisfactory operative result then faces only three further obstacles. These are, respectively, failure to want fusion, failure to recognize the difference between fusion and single vision by suppression (or by anomalous correspondence, or by the Swan blind-spot syndrome), and, finally, failure to get comfort out of fusion, which may mean that more surgical correction is indicated. Miss Lancaster calls attention to the fact that sometimes a patient is referred for orthoptic training because the surgery did

not turn out as the ophthalmologist had expected or hoped and he would like to have an unsuccessful result corrected by orthoptic training. If the operation left the patient with obstacle 1, i. e., inability to move his eyes so as to get simultaneous perception at corresponding points, then such a patient is no more ready for postoperative orthoptic training than if he had had no surgery at all. It is obvious that the patient should have adequate surgical correction before sensory fusion is expected of him. The question of preoperative orthoptic training is also considered. The point that the author emphasizes is the difference between orthoptic training in cooperation with surgery, where it can be of help, and orthoptic training which is expected to compensate for surgical errors, which it can seldom do, and which the ophthalmologist should not expect it to do. The question of how soon orthoptic training should follow surgery is answered by Miss Lancaster in terms of weeks or months. She feels that there is no hurry for postoperative training, and that it is better to wait until all soreness has disappeared from the eyes as a result of the operation, but that a wait of over six months is inadvisable unless the patient is too young to profit by orthoptic training. In such cases, waiting is obviously necessary, and training may be given intermittently as fast as the patient is able to absorb it.

The second half of the book deals with practical orthoptics. An orthoptic analysis is chiefly concerned with the functioning of the two eyes together. This includes changes in visual acuity during treatment; the control of accommodation; measurements of the deviation under different conditions; status of the retinal correspondence, and a study of suppression habits, measurements of the amplitude of fusion, and evaluation of the patient's ability to profit by orthoptic training. Each of these is given due consideration, with particular emphasis on the status of suppression, which the author insists is one of the most important tasks the orthoptist has.

The various means which the technician may employ to break down suppression are described in detail. The last chapters deal with specific problems, such as accommodative squints and the influence of anomalous correspondence on the patient's progress.

The reviewer believes that this book should be studied by every ophthalmologist. It will give him a much better insight into the aims of orthoptics and will help to dispel some fallacious notions which tend to discredit orthoptics, and which are frequently due to misconceptions of the ophthalmologist as to the part played by orthoptics in the treatment of squint.

Ophthalmology. By Arno E. Town, M.D., Professor of Ophthalmology, Jefferson Medical College of Philadelphia. Price, $10. Pp. 511, with 208 illustrations and 4 colored plates. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1951.

This volume, designed for medical students and general practitioners, represents the combined efforts of the author and his eleven contributors. While it contains much valuable information, some of which is not found in most standard textbooks, it lacks continuity. The various aspects of ophthalmology are not presented in a uniform manner. Some subjects, such as the physiology of vision, are given in considerable detail, while others, of more practical value, are briefly reviewed. This is particularly noticeable in the chapters on extraocular muscles and the correction of optical defects. The diseases of the orbit, lachrymal apparatus, conjunctiva, and uvea are sufficiently comprehensive, but the tabulation of the salient features of specific corneal diseases is too brief to enable the student to gain a mental picture of the various types of keratitis. The subject of glaucoma is well discussed, and the characteristics of the three types of primary glaucoma are given in a concrete manner. The latter feature will appeal to the student. Correct emphasis has been placed upon the use of the ophthalmoscope, and the chapters dealing with the diseases of the interior of the eye are clearly written and amply illustrated. The section on neuro-ophthalmology contains full descriptions of most of the diseases with which the general physician will be confronted and constitutes

an important part of this book. Innovations which will be of great value to the general practitioner are the outlines on the ocular changes found in various general diseases, on symptomatic diagnosis, and on standing orders for traumatic cases in industrial dispensaries.

The Adjustment of the Blind. By Hector Chevigny and Sydell Braverman. Price, $4. Pp. 320. Yale University Press, 143 Elm St., New Haven 7, Conn., 1950.

The purpose of this book is to tell us how the blind act, feel, and think, and to dispel the numerous fallacies which have come down to us as a heritage from antiquity. The authors point out that beliefs having little to do with common experience have grown up about the emotions of the blind. These erroneous ideas have much to do with the intolerable methods by which the blind have been treated in the past, at first being reduced to beggary and then literally incarcerated in asylums, where they became objects of pity, or at least where the rest of the world did not have the necessity of seeing them and trying to solve their problems.

Considerable space is spent in giving this historical background. The methods by means of which the blind, aided by those few persons who tried to help them, have sought to rehabilitate themselves, are carefully traced, and one is amazed to learn of the struggles, which often became bitter between various factions, who could not come to agreement even on such simple things as which was the best form of Braille.

Probably for the first time, the way in which the blind think and react to the seeing world is described in detail. The fact that the book was written by a person who went blind, and who previously was a well-known author and at one time chief of the script division of the Columbia Broadcasting System in Hollywood, together with a clinical psychologist, makes this part of the book authoritative.

There is no question that all ophthalmologists should read this book. The reviewer was constantly being embarrassed, when references were made to the correct and the incorrect handling of situations with the blind, by the numerous times in which he had stupidly taken the wrong course. The authors mince no words in calling attention to the fact that ophthalmologists in general are prone to let the patient go his own way as soon as blindness appears on the scene. The following quotation exemplifies this: "The influence of the ophthalmologist is ordinarily reckoned in terms of his success or failure at restoring sight. At the point of permanent loss of sight he disappears from the picture. His influence would, therefore, seem to be incidental." If, on reading this book, we as ophthalmologists are aware of a certain feeling of resentment toward our stupidity, and that certain pages are tinged with bitterness, we shall have to admit that we have brought it on ourselves through ignorance. This book will go a long way toward dispelling that ignorance.

Clinical Pathology of the Eye. By Bernard Samuels, M.D. and Adalbert Fuchs, M.D. Price, $20.00. Pp. 420, with 418 illustrations, 191 in full color. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33 St., New York 16, N. Y., 1952.

The student who wishes an introduction to ophthalmic pathology will find Samuels' and Fuchs's textbook a practical and orthodox treatise. The arrangement is the standard one of first considering pathologic processes in general, then separately considering diseases of the anatomic parts of the eye, and finally describing some of the specific disease entities. Especially deserving of comment are the many beautiful colored plates of drawings, which the authors have preferred to photomicrographs to "emphasize the details in hand." The authors have drawn on their wide experience in Vienna and New York, adopting much of the techniques and many of the ideas that have been found successful in teaching ophthalmic pathology over the last half-century.

The student who wishes to go beyond the introduction to ophthalmic pathology will find this book unsatisfactory. Source material is not cited, and the authority for many of the opinions and statements is not given. The newer concepts of pathophysiology and histochemistry are wanting. These have, no doubt, been purposively omitted in the interest of brevity and simplicity, for the book is intended not for the ophthalmic pathologist but, rather, as stated in the preface, for the ophthalmologist, general practitioner, and surgeon. To this end it should serve an eminently useful purpose.

CORRECTION

In the article entitled "Orbital Pseudotumors" by Thomas W. Cowan, M.D., published in the October, 1951, issue of the ARCHIVES, page 390, W. J. Hope-Robertson (footnote 2) was incorrectly referred to as W. J. Robinson.

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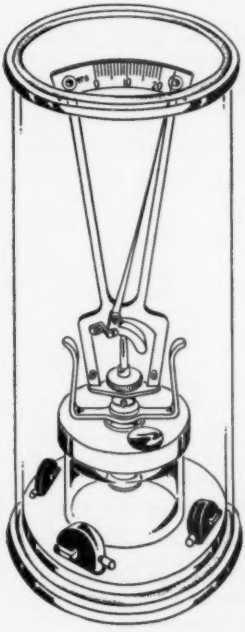

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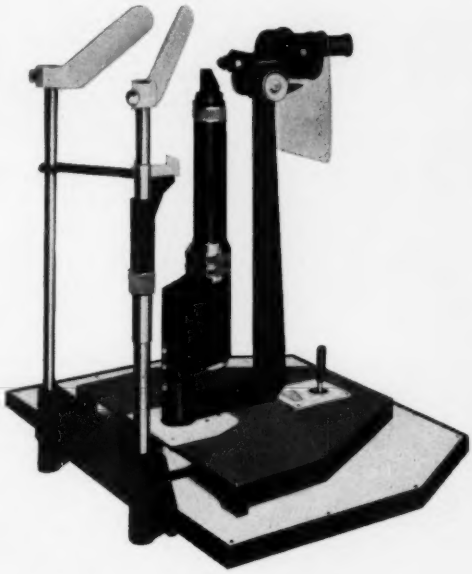

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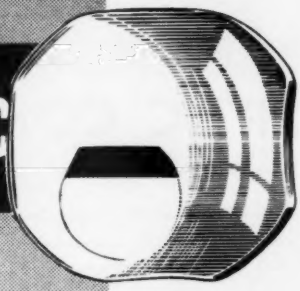

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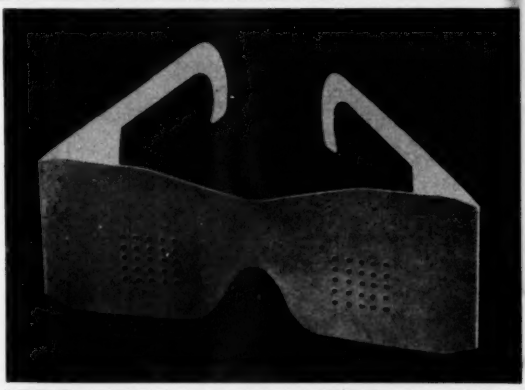

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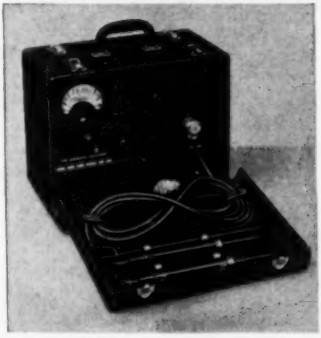

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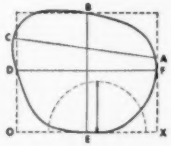

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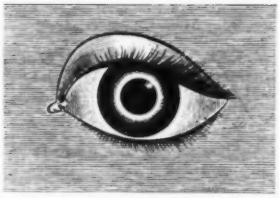

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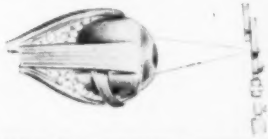

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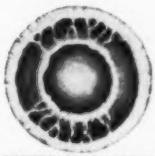

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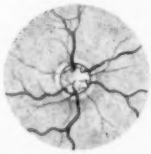

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